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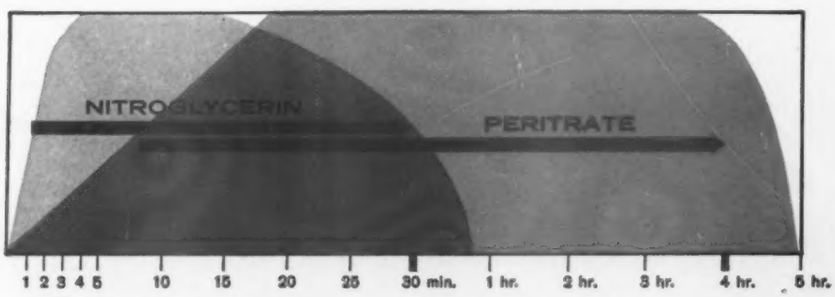
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The Munchausen Syndrome or the Problem of Hospital Hoboes
EDWIN CLARKE AND S. C. MELNICK 6

Here is a report not cast in the common mold, from which the reader will derive as much pleasure as profit. The subjects recorded are well known to every hospital physician but seldom so well studied and described—hospital hoboes, as the authors happily designate them. Let the physician beware!

The Barrel Deformity of the Chest, the Senile Lung and Obstructive Pulmonary Emphysema . . . . . JOHN A. PIERCE AND RICHARD V. EBERT 13

The authors demonstrate what has long been suspected, that the designation "senile emphysema" given to elderly patients with barrel deformity of the chest is inappropriate since pulmonary function studies give no indication of obstructive emphysema. It is shown quite convincingly that there is no functional difference between the senile lung and barrel deformity of the chest.

Pulmonary Compliance in Granulomatous Disease of the Lung . HAROLD A. LYONS 23

In view of the extensive interstitial infiltration encountered in pulmonary granulomatosis, a reduction in the "stretchability" or compliance of the lung would be expected. In this study of twenty-nine cases of pulmonary granulomatosis, particularly of sarcoidosis, the author uniformly found such a reduction. The diminution in compliance was well correlated with reduction in total lung capacity and vital capacity, and was associated with reduction in arterial oxygen saturation in all but four patients. Evaluation of the results of cortisone therapy revealed return of pulmonary compliance toward normal, associated with clinical improvement.

The Rapid Diagnosis of Ventilatory Failure with the Carbon Dioxide Analyzer
DONALD E. GRIGGS, JACK D. HACKNEY, CLARENCE R. COLLIER AND JOHN E. AFFELDT 31

Recognition of alveolar hypoventilation and hypercapnia is an increasingly important clinical problem. Moreover, quantitation of the increase in the tension of carbon dioxide in the arterial

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- postoperatively
- in pregnancy when vomiting is persistent
- following neurosurgical diagnostic procedures
- in infections, intra-abdominal disease, and carcinomatosis
- after nitrogen mustard therapy

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blood is particularly important in the management of known cases of ventilatory failure, the uncovering of unsuspected cases, and in evaluating the responses, good and bad, to the therapeutic measures employed. The authors present a method of rapid bedside diagnosis of increase in arterial carbon dioxide tension, utilizing an infra-red CO_2 analyzer to determine CO_2 levels obtained during re-breathing. The use of these measurements in the diagnosis and management of ventilatory failure is illustrated by representative cases.

Studies on the Regulation of the Coronary Circulation in Man. I. Atropine-induced Changes in Cardiac Rate

RICHARD GORLIN WITH THE TECHNICAL ASSISTANCE OF MORRIS H. SMITH AND HERBERT P. FLETCHER 37

It has been frequently suggested that marked tachycardia in man may be deleterious to both coronary circulation and cardiac function. These careful studies utilizing catheterization of the coronary sinus in six patients reveal that increase in heart rate, either spontaneous or atropine-induced, results not only in decreased diastolic filling of coronary vessels, but also in increase in myocardial oxygen consumption and coronary flow. The increase in flow is made possible by the concomitant reduction in coronary vascular resistance. These studies would suggest that in pathological states in which such reduction in resistance may not be possible, increase in myocardial demand for oxygen induced by marked tachycardia may lead to coronary insufficiency and to heart failure.

Analysis of Factors Affecting the Recurrence of Thromboembolism off and on Anticoagulant Therapy

STEFAN A. CARTER, ELLEN MCDEVITT, BARBARA W. GATJE AND IRVING S. WRIGHT 43

While short-term anticoagulant therapy for thromboembolism has become general policy, when contraindications are absent, it has yet to be demonstrated that long-term anticoagulation for prevention of recurrence of thromboembolism confers more benefits than the difficulties and hazards it imposes, except under the most favorable conditions. The present study is a statistical analysis of the results in patients followed up at least six months off and six months on anticoagulant therapy. Statistical evidence of benefit was obtained, but this was of borderline significance in patients with congestive heart failure, atrial fibrillation, myocardial infarction, and the like. The tendency to thromboembolism increased within the six-week period following discontinuance of anticoagulant prophylaxis. It would seem that more data on this important subject will be required before definite conclusions can be reached.

Nodular Panniculitis after Massive Prednisone Therapy

ANGELO TARANTA, HERBERT MARK, RAYMOND C. HAAS AND NORMAN S. COOPER 52

The authors make an interesting observation of the occurrence of a nodular panniculitis resembling Weber-Christian syndrome when prolonged administration of large doses of prednisone was discontinued—another hazard of steroid therapy. If this complication is looked for more pointedly, additional examples may well be found.

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AN AMES CLINIQUICK
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which patients with noncalculous gallbladder disease should undergo surgery?

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Reviews

The Pathogenesis of Pulmonary Emphysema . . . . . K. H. McLEAN 62

This thoughtfully executed and lucidly described study of emphysema admirably illustrates the importance, for clear understanding of normal and abnormal function, of a detailed knowledge of morphology. The author begins with a description of the normal anatomy of the respiratory tract as an airway terminating blindly in alveoli which, however, intercommunicate by means of alveolar pores. The role of acute bronchiolitis is next described, and its part in the development of bronchiolar obstruction and of air-trapping, even in the collaterally ventilated lung. This, together with changes in the elasticity of the bronchiolar walls and other factors, gradually results in the physical and functional abnormalities of obstructive emphysema. The progress of events as thus described does not conflict with current views but more clearly relates the several etiological forces to the clinical end-result.

Treatment of Tuberculosis Today. A Five Year Report . . . ALBERT R. ALLEN 75

It is well recognized that the introduction of antituberculous chemotherapy, and the liberalization of surgical resection that this made feasible, have greatly improved the prognosis of the tuberculous patient. The present analysis of a long-term large-scale program in a large tuberculosis hospital recounts the details of this impressive advance. The combating of drug resistance, the indications for surgical resection, the shortening of hospital stay, the increased incidence of cure and decreased incidence of contagion and reactivation, the importance of follow-up, are all vividly described, The author emphasizes the point that simply administering drugs is not enough, nor is hospitalization of itself sufficient for optimum treatment—this requires alertness to the proper needs of the individual patient under the constant supervision of hospital care. And with all this, he adds, despite the fall in the tuberculosis death rate the number of new cases discovered each year and the extent of the disease in the new cases uncovered thus far shows no distinct decline.

Seminar on the Brain

Pathologic Physiology of Cerebral Dysfunction . . . . . JOSEPH F. FAZEKAS 89

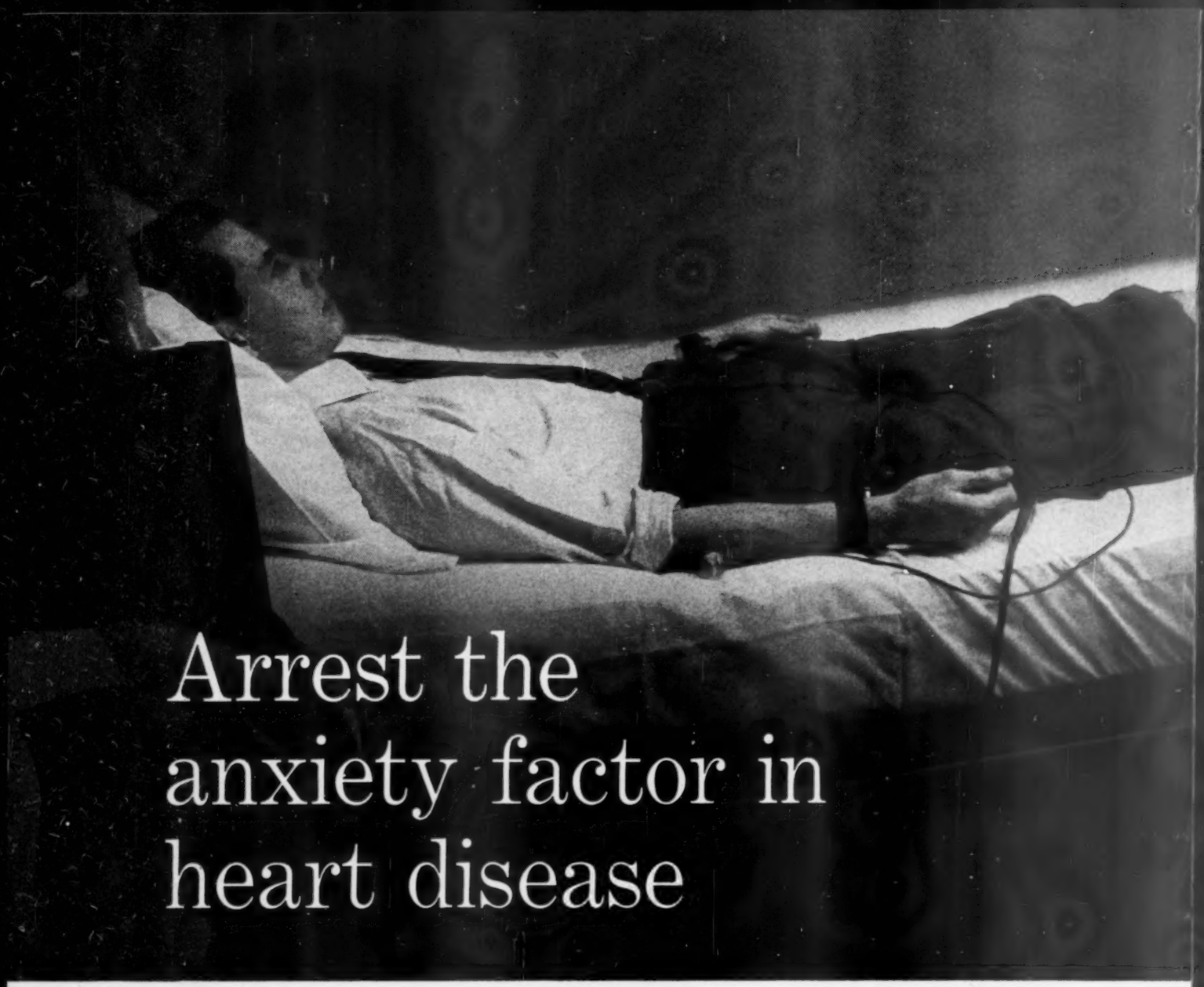
Dr. Fazekas' opening contribution to the seminars on the brain serves admirably to orient the reader in relation to the physiologic aberrations of greatest current interest. In the case of "organic" brain disorders, these abnormalities are, by definition, overt. They are sequentially considered as being due to substrate (glucose) insufficiency, oxygen insufficiency, impairment of enzyme (or coenzyme) activity, and disordered energy utilization. In the case of "functional" disturbances of the central nervous system the abnormalities are, by definition, occult. Nevertheless, the implied impairment of integration of neuronal activity suggests some underlying metabolic aberration, possibly in energy utilization. A consideration of the chemical mediators in the central nervous system, and of the action of neuropharmacologic agents, throws some light on these relationships.

Clinico-pathologic Conference

Polycythemia Vera, Compression Fractures and Hyperuricemia 97

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An interesting case, well studied and discussed in informative detail.

Adult Agammaglobulinemia Associated with Multiple Congenital Anomalies SAMUEL ZELMAN AND HANS LEWIN 150

The case is unusual and the discussion of interest.

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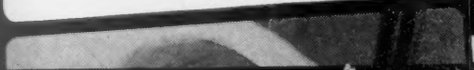
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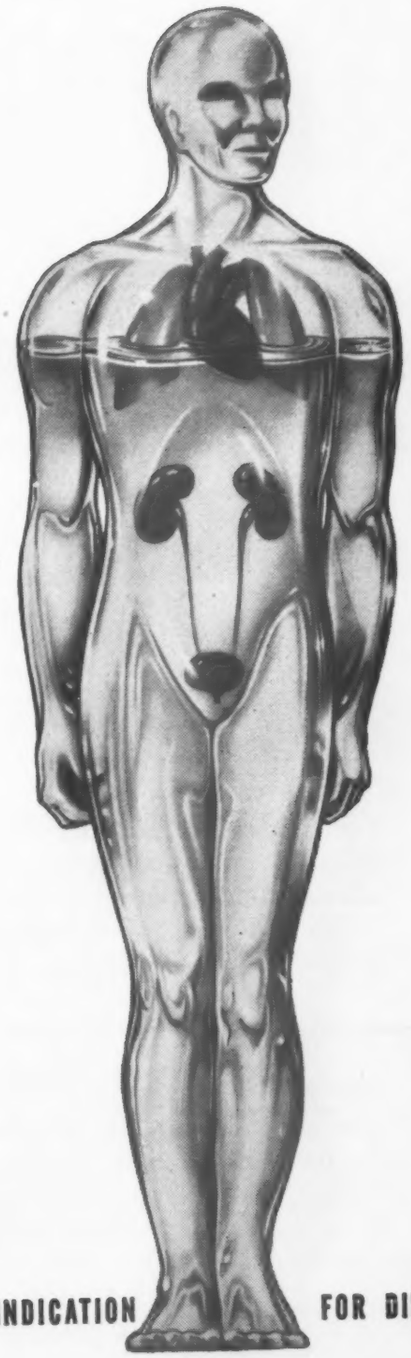
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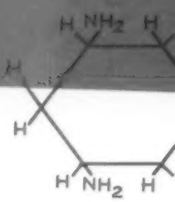
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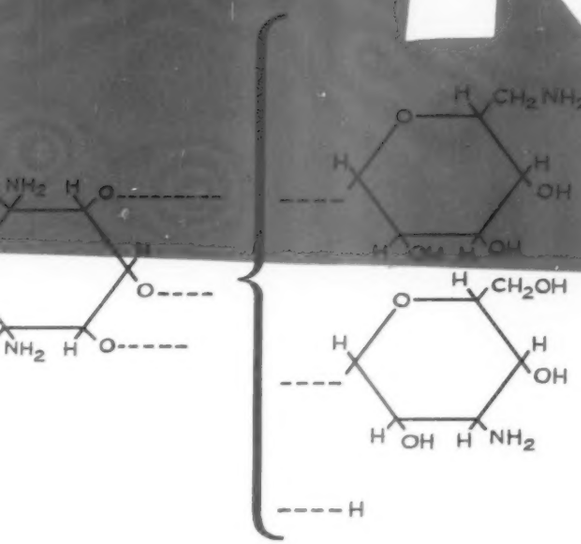
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The patient was discharged as recovered on 2/7/58, and a clinical follow-up since then showed him to be entirely well. This case was described by the investigator as "a therapeutic triumph."

---

*Sol Katz, District of Columbia General Hospital, Washington, D.C.: Personal communication.



Among the pathogenic organisms susceptible to KANTREX are various strains of *Staph. aureus* and *albus, Proteus, A. aerogenes, Klebsiella pneumoniae, Salmonella, Shigella, E. coli, paracolobacterium, Pseudomonas* and *enterococcus.*

Preliminary studies indicate that KANTREX is a promising agent against *Mycobacterium tuberculosis,* including streptomycin- and isoniazid-resistant strains.



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Kanamycin Sulfate

Indications

Indications for KANTREX include infections due to kanamycin-susceptible organisms:

Respiratory infections: laryngitis, tracheitis, bronchitis, pneumonitis, broncho-pneumonia, lung abscess, pleuritis, empyema and bronchiectasis.

Urinary tract infections: acute and chronic pyelonephritis, cystitis.

Soft tissue infections: wound infections, abscesses, cellulitis, osteomyelitis, blood stream infections.

Dosage

Adults: Average daily intramuscular dose 1 to 2 Gm. in 2 to 4 equally divided doses.

Children: Average daily intramuscular dose 15 to 30 mg. per Kg. in 2 to 4 equally divided doses.

Precaution

In the course of extensive clinical trials, signs of renal irritation and skin eruptions (which disappeared on cessation of therapy) were occasionally noted. Signs of eighth nerve dysfunction—tinnitus, vertigo and loss of hearing—were observed in a few patients. These patients were predominantly over forty-five years of age; all had received 18 grams or more of KANTREX. In this latter respect it would appear that KANTREX has less toxic potential than streptomycin.

Supply

KANTREX is available in rubber-capped vials as a ready-to-use sterile aqueous solution in two concentrations (stable at room temperature indefinitely):

KANTREX (kanamycin sulfate) 0.5 Gm. in 2 ml. volume.

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Also available: KANTREX (kanamycin sulfate) Capsules, 0.5 Gm. for preoperative bowel antisepsis; bottles of 20 and 100.

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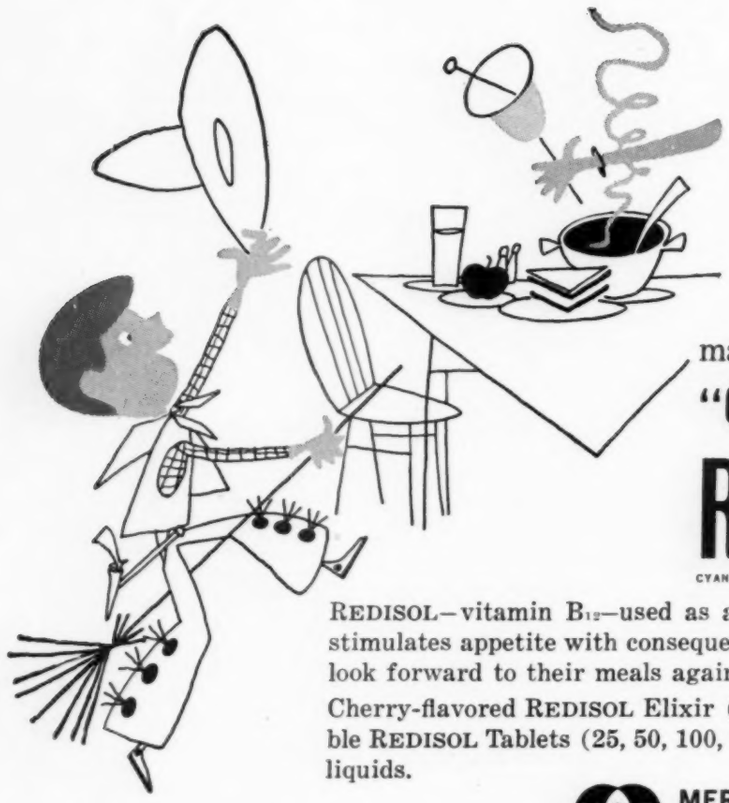
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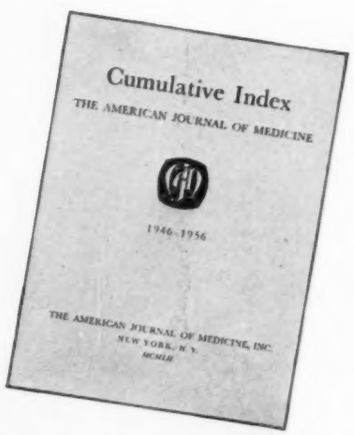
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1. *Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Card.* **1**:395, March 1958.
2. *Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology* **8**:504, Dec. 1957.

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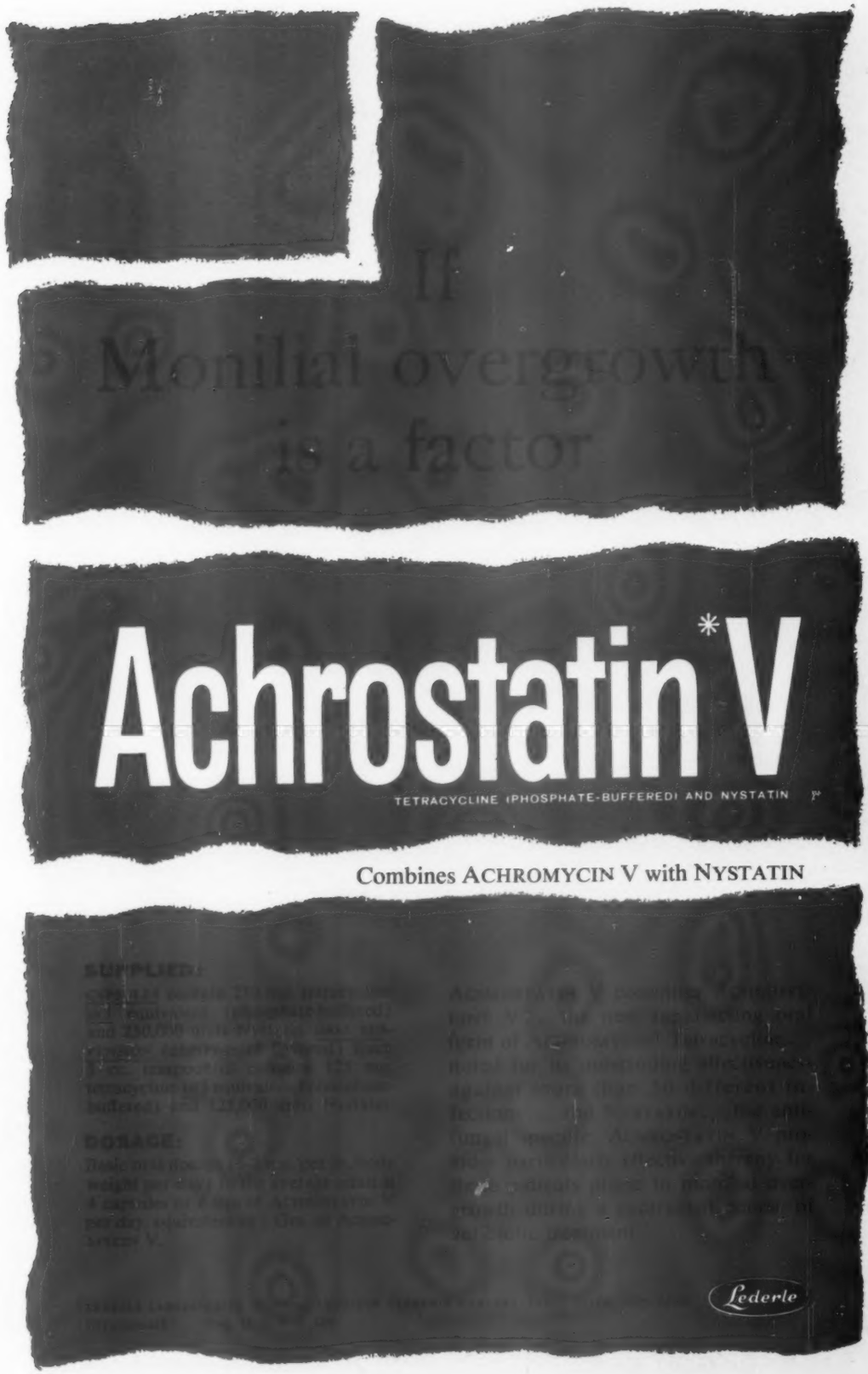
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1. Murphree, H.B. Jr.; Jenney, E.H., and Pfeiffer, C.C.: Presented before Assoc. for Research in Nervous and Mental Disease, New York, Dec. 12-14, 1957. To be published.

In Exhaustion and Depression—In a study of over 100 patients suffering from various psychiatric disorders, especially exhaustion and mild depression, the clinical effect of 'Deaner' was to increase energy and to relieve depression in over 70%.

2. Lemere, F., and Lasater, J.H.: Am. J. Psychiat. *114*:655 (Jan.) 1958.

In Learning Problems—Some of the children with reading problems and other learning defects have improved markedly during their treatment with 'Deaner'.

3. Oettinger, L.: To be published.

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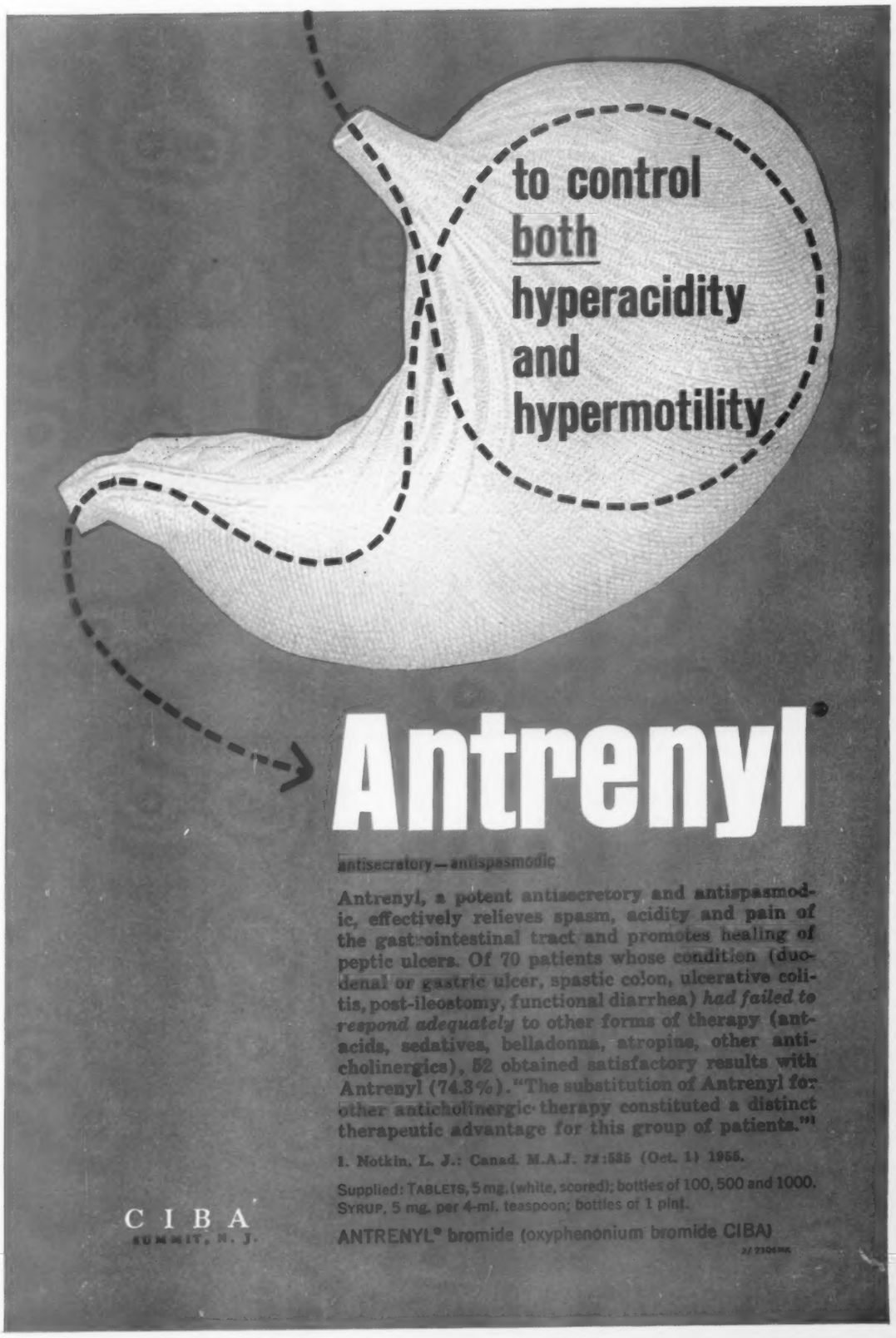
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1. Notkin, L. J.: Canad. M.A.J. 73:535 (Oct. 1) 1955.
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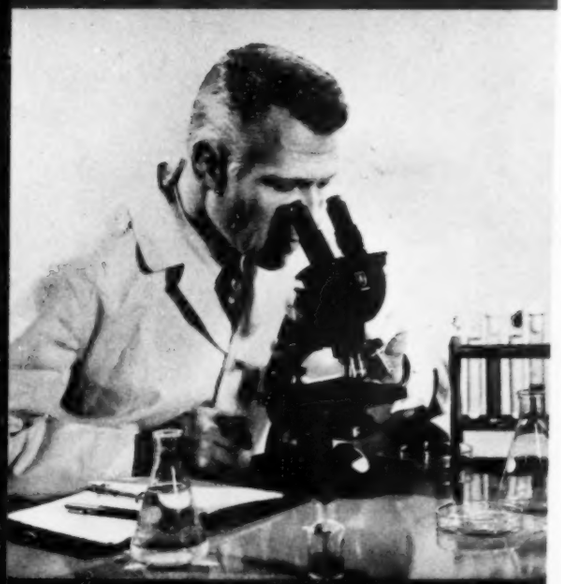
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*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition *1*:35 (Jan.-Feb., 1957).

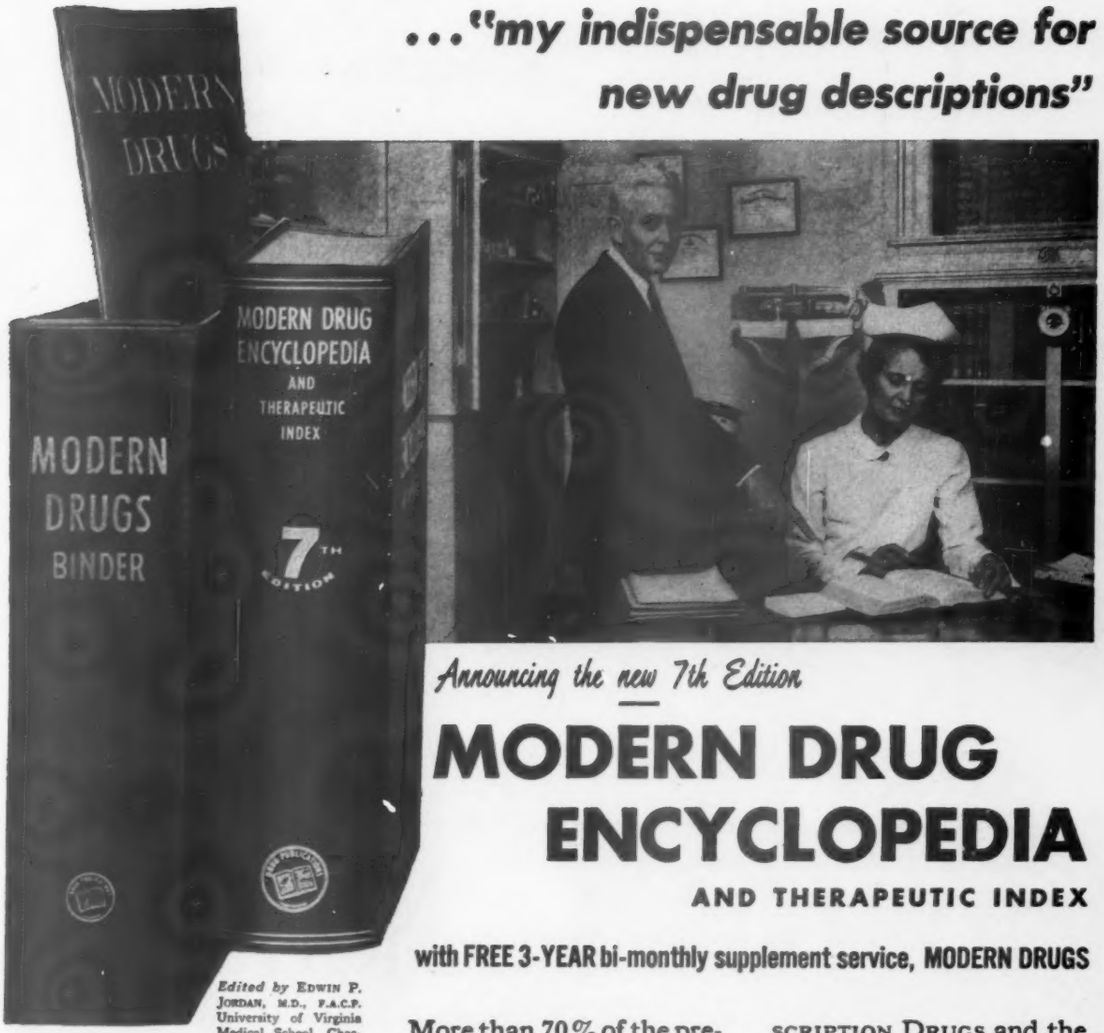
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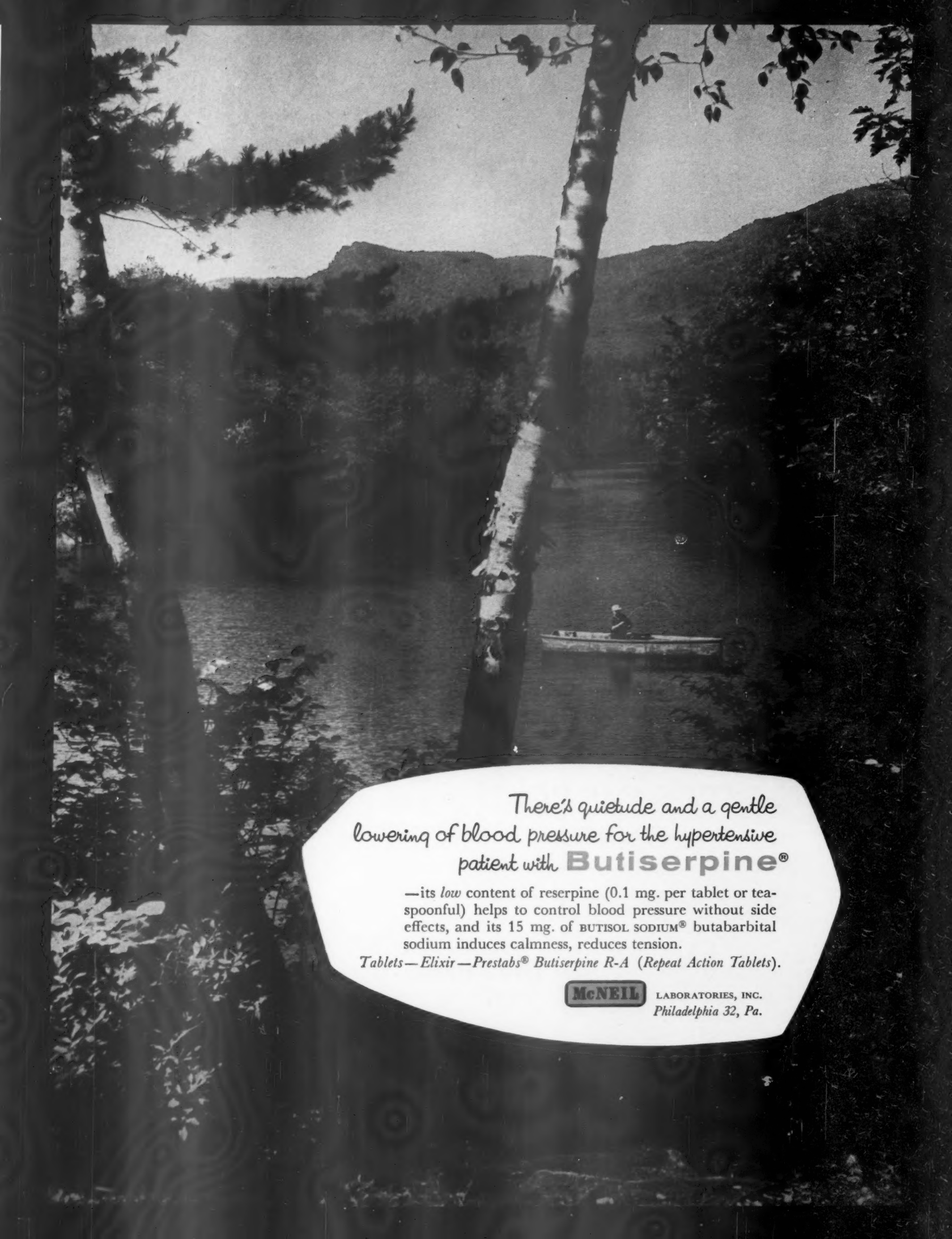
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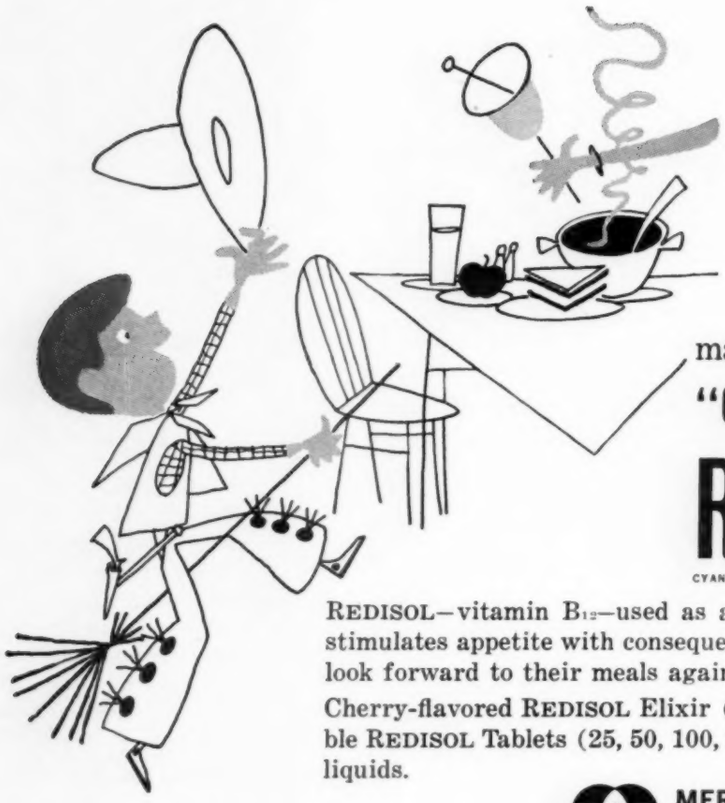
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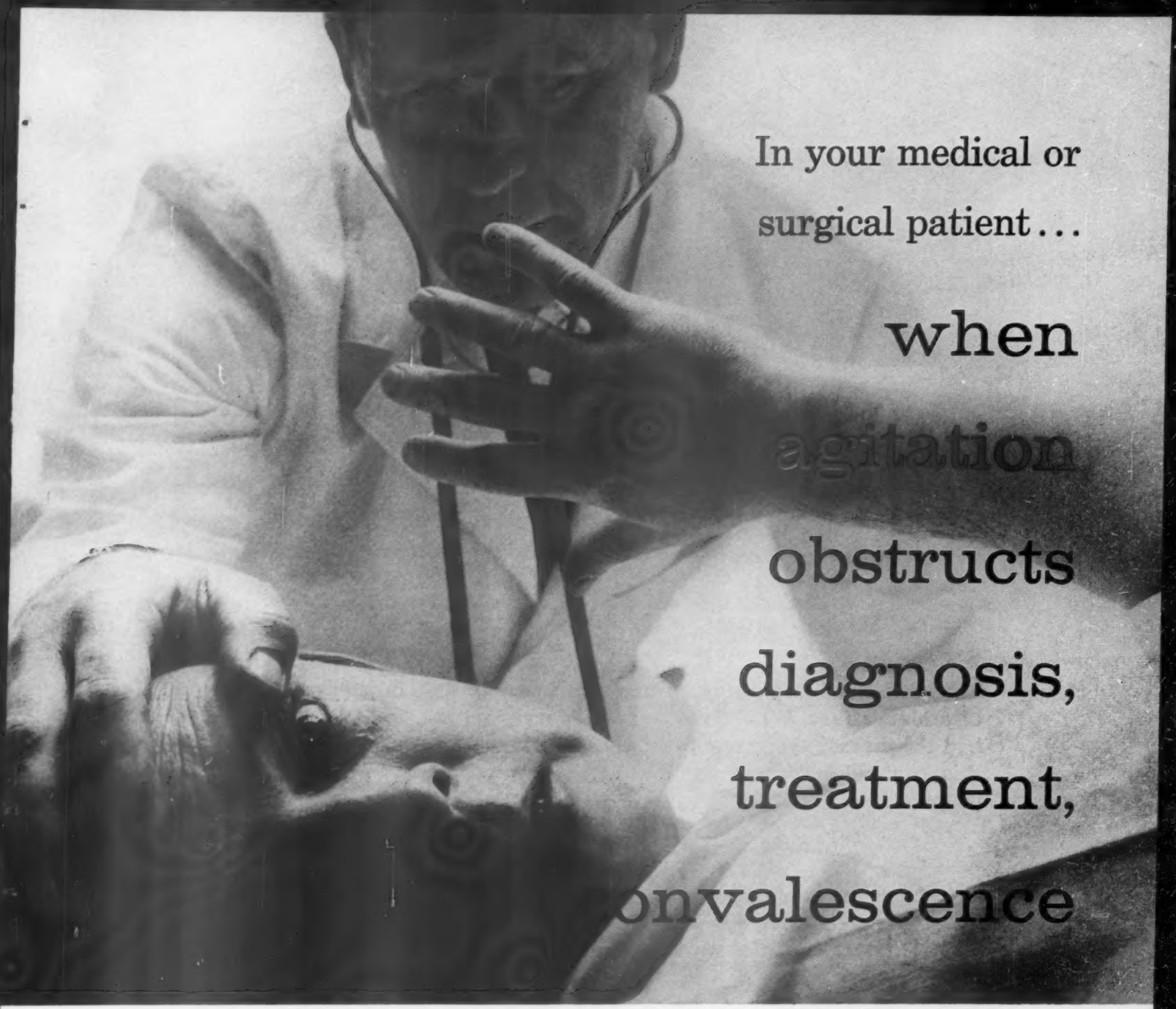
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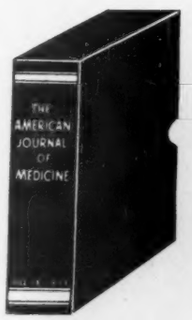
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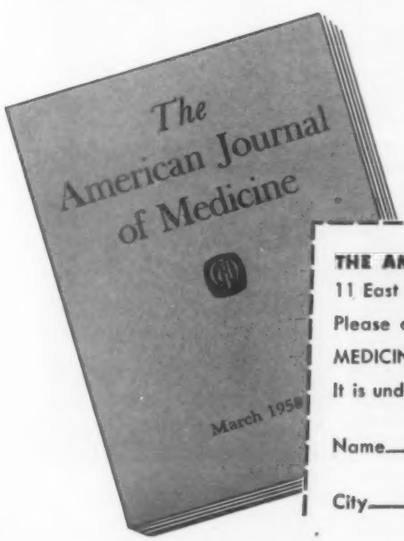
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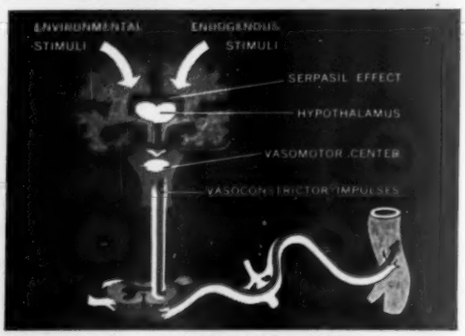
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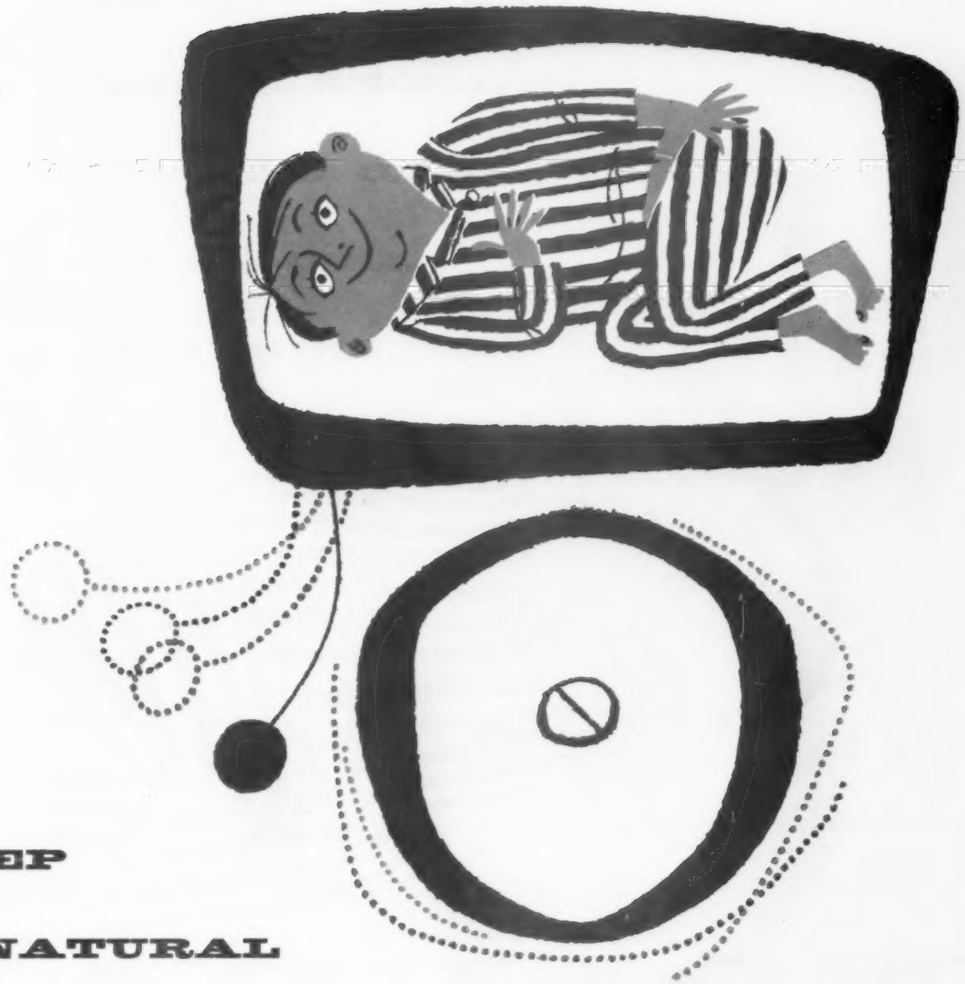
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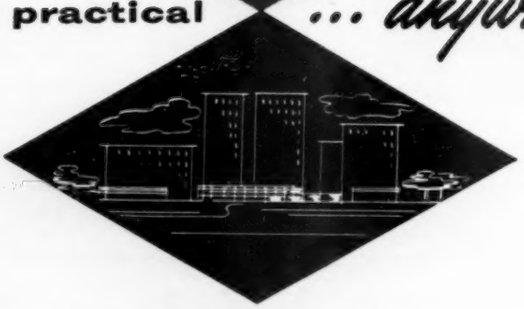
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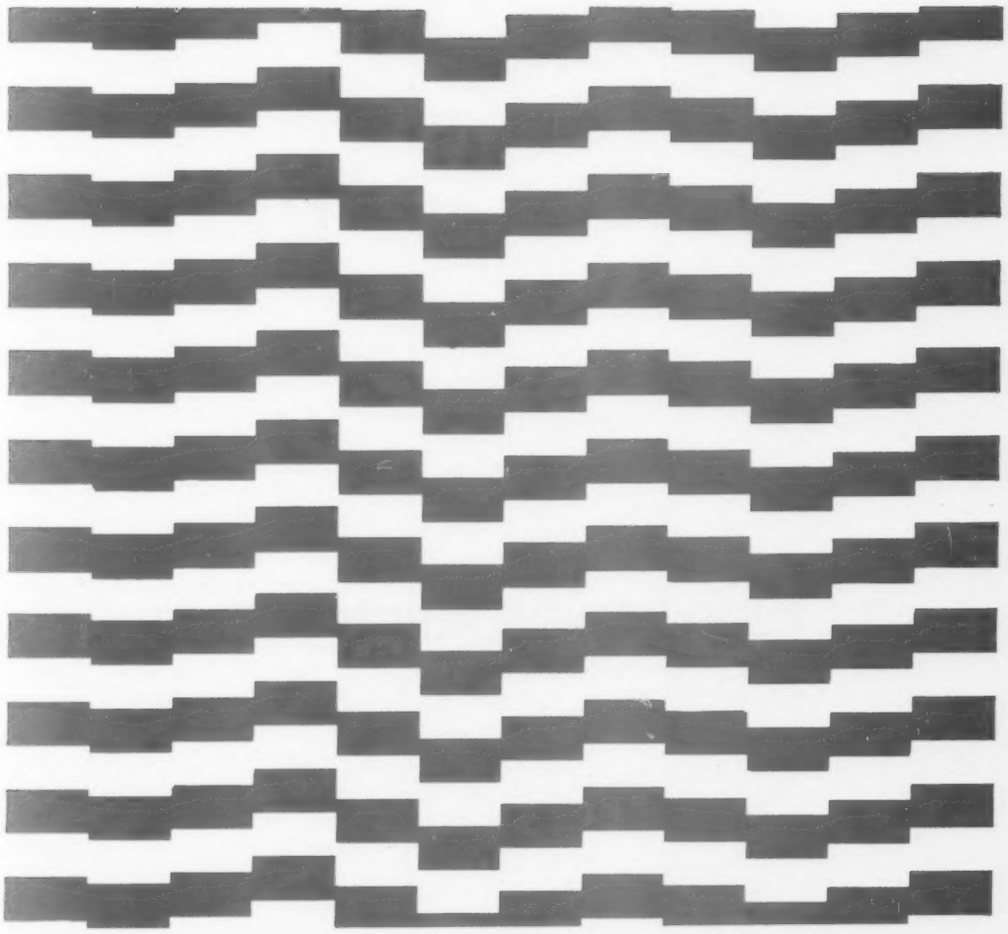
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1. Campbell, D. G.: In: *Modern Nutrition in Health and Disease*, Wohl, G. M. and Goodhart, R. S. (Editors), Lea & Febiger, Philadelphia, 1955, p. 814.

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1. Shalowitz, M.: Geriatrics 11:312, 1956. 2. Warter, P. J.: J. M. Soc. New Jersey 54:7, 1957. 3. Hutcheon, D. E., et al.: Paper presented at Am. Soc. Pharmacol. & Exper. Therap., Nov. 8-10, 1956, French Lick, Ind. 4. Strub, I. H.: To be published. 5. Individual Case Reports to Medical Dept., Pfizer Laboratories.

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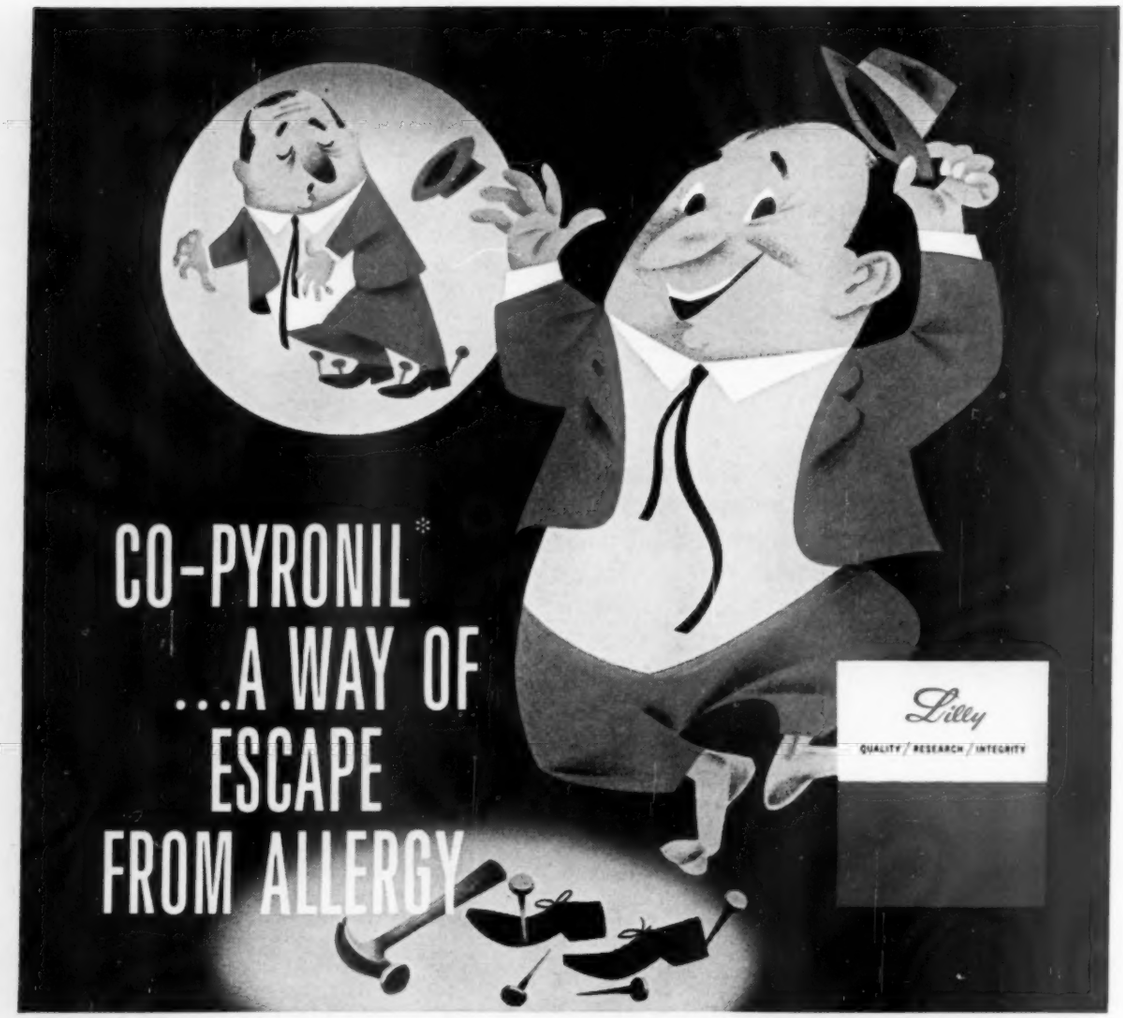
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Editorial

Hydrogen Ions and Buffer Base

THE past few years have witnessed a considerable ferment in acid-base terminology as well as renewed interest in the physiological aspects of the subject. A series of writers [1–7] have stressed the idea that much confusion may be avoided by adhering to the Bronsted definitions, in which the term "acid" is restricted to hydrogen ion (proton) donors and "base" to hydrogen ion acceptors. Even the partial step of substituting "anion" for "acid" and "cation" for "base," while minimizing the confusion, has been deemed inadequate, and acid-base equilibrium has been restated in terms of hydrogen ion alone. This has been a useful emphasis because it has often been forgotten that other methods of describing acid-base changes are dependent upon the fact that they indicate certain equivalent transfers of hydrogen ion.

Nevertheless, in a semantic onslaught against an "archaic" clinical usage, concepts may suffer. It must be stressed that the factors involved remain the same and that the clarification is in terminology only. If this is overlooked, the baby, so to speak, is in danger of being thrown out with the bath water. The traditional clinical use of "fixed acids" and "fixed bases," as developed by such pioneers in the field as Henderson, Van Slyke, Stadie, Peters and Gamble, can hardly be said to have arisen in ignorance. It was evident, and still should be, that hydrogen ion concentration *alone* (or its logarithmic expression, pH) is not an adequate index of the physiological processes involved in acid-base disturbances. If a large quantity of hydrogen ion is added to, or removed from, a phase of the body fluids, only an extremely minute fraction remains unbuffered. This concentration during life cannot exceed the order of magnitude of one ten-thousandth to one-hundred thousandth of a milliequivalent per liter. True, the concentration of *free* or dissociated hydrogen ion, although small in absolute quantity, is of great physiological importance. But it is also important, especially when considering therapy, to measure the vastly larger change "hidden" by buffering, which is not predictable from changes in pH alone.

Thus rigid adherence to a unitary system expressed in terms of hydrogen ion may avoid some confusion, but it does not mean that one can disregard other ions. It simply drops the "short cuts" and adds the additional step of converting from the ionic changes measured to the accompanying alterations in hydrogen ion. It is still necessary to appreciate the *relationship* between changes in hydrogen ions and changes in other ions, and to distinguish between "fixed

[1] CHRISTENSEN, H. N. Control of the hydrogen ion. *New England J. Med.*, 247: 174, 1952.

[2] DEVOR, A. W. Bronsted theory applied to acid-base balance and respiration. *J. Chem. Educ.*, 31: 425, 1954.

[3] RELMAN, A. S. What are "acids" and "bases"? *Am. J. Med.*, 17: 435, 1954.

[4] CHRISTENSEN, H. N. Anion-cation balance? *Univ. Michigan M. Bull.*, 22: 163, 1956.

[5] KAUFMAN, H. E. and ROSEN, S. W. Clinical acid-base regulation—the Bronsted schema. *Surg., Gynec. & Obst.*, 103: 101, 1956.

[6] SCHWARTZ, W. B. and RELMAN, A. S. Acidosis in renal disease. *New England J. Med.*, 256: 1184, 1957.

[7] CHRISTENSEN, H. N. Anions versus cations? *Am. J. Med.*, 23: 163, 1957.

ions" and "buffer ions." Once the necessary relations are understood it is often convenient to use directly the terms measured. These changes in other ions usually have developed as a result of the same reactions that caused the original change in hydrogen ions or an immediate buffering reaction that simultaneously changed hydrogen ions. In either case they may be properly considered to be "the other side of the coin" rather than merely secondary effects of the transfer of hydrogen ion. Measured in this way, the disturbance can be determined in chemical equivalents so that *total contents* in body fluid compartments, as well as concentration, may be estimated. Far from being unrelated or secondary effects, alterations in other anions and cations constitute a framework for consideration of acid-base balance in quantitative terms; this holds true whether or not the results are then expressed as changes in hydrogen ion.

What then is to be the basis for relating such ionic changes to acid-base problems and for distinguishing them from electrolyte disturbances without acid-base effects? Is there any key to the confusion and conflicting terminology? We believe that there is. In our opinion the most satisfactory method is the application of the "buffer base" index of Singer and Hastings [*8*]. It provides a method of measuring the most meaningful changes in hydrogen ion and of distinguishing non-respiratory ("metabolic") from respiratory disturbances. It emphasizes that a change in a *single* ion cannot be interpreted in acid-base terms. But, at the same time, if accompanying alterations in other ions are known, this concept furnishes a method of grasping the contribution of each to total non-respiratory acid-base change as well as a method of quantitating such change without determination of all the individual components.

The Buffer Base Concept. Actual change in hydrogen ion concentration in equivalent terms is so small relative to buffer changes that it can be neglected, and the latter regarded as expressing a total non-respiratory acid-base disturbance. Respiratory disturbances may cause a redistribution of buffer between bicarbonate and non-bicarbonate buffer, without affecting total buffer. Singer and Hastings [*8*] developed the most practical method for determining the value for the total buffer change in blood without necessarily measuring its individual ionic components. The numerical value is customarily determined from their nomogram using the measured values for the plasma pH and plasma or whole blood CO_2 content.* To appreciate the utility and meaning of the concept it is best, however, to consider this total buffer change in terms of its ionic components. Indeed, the nomogram itself was derived as an approximation from the following concepts. The rationale behind certain clinically useful expressions for approximating the total change will also become evident.

"Buffer anions" are those anions whose concentrations are affected by pH changes in the physiological range. Because of the effect of excretion of CO_2 by the lungs it is useful to divide blood buffer anions into bicarbonate and non-bicarbonate buffer anions, designated herein as HCO_3^- and Buf^-, respectively. The most important component of the latter consists of anions of hemoglobin; also included are anions of plasma proteins, organic phosphate of red cells and small quantities of other buffers.

Let us now consider as an example of "metabolic acidosis" the addition of hydrogen ion to the body. Both of the following two fundamental equilibrium equations are immediately driven toward the right:

$$H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2\uparrow \qquad \text{Equation (1)}$$

$$H^+ + Buf^- \rightleftharpoons H\,Buf \qquad \text{Equation (2)}$$

The added hydrogen ion has almost completely disappeared, but simultaneously it has reduced the total buffer anions to a numerically equal degree; it is necessary however to summate the change in both buffer anion components to recognize the total added (and buffered) hydrogen ion. The total buffer anions are expressed numerically as "buffer base" (designated by the symbol BB). The use of the word "base" stresses the fact that this numerical value moves in the opposite direction from the disturbing hydrogen ion change. The term "buffer base" is brief and specific, has not been in use in conflicting senses, and is appropriate whether

[8] Singer, R. B. and Hastings, A. B. An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. *Medicine*, 27: 223, 1948.

* A hematocrit value must also be used or assumed as an approximation. While pH and CO_2 content are more commonly used, it is also possible to substitute determined arterial CO_2 pressure (or, as ordinarily almost identical, alveolar air CO_2 pressure) for either of these terms—preferably of course for the CO_2 content.

"base" is defined by the Bronsted theory or by traditional clinical terminology.*

"Fixed ions" are the non-buffer ions; their respective concentrations are not affected by pH changes in the physiological range. Because blood contains no measurable "buffer cations," the buffer term is all on one side of an ionic diagram and is also numerically equal to the difference necessary to maintain electroneutrality between fixed cations (B^+) and fixed anions (A^-). Thus BB is a numerical relationship directly associated with hydrogen ion changes that are no longer present as such in the body and is visualized conveniently in terms of *either* buffer or fixed ions, as illustrated in Figure 1, modified from Singer and Hastings. These are alternative ways to arrive at the same value and for this purpose one never uses both fixed and buffer ions in the same expression.

A respiratory disturbance behaves differently. Consider retention of CO_2 in the body, driving Equation (1) toward the *left*. Virtually all the hydrogen ion so liberated is now buffered by the reaction of Equation (2) moving to the *right*. Thus the increase in HCO_3^- is offset by an equal decrease in Buf^- and there is no change in BB. Of course secondary responses or other factors may cause some change in BB, but these are then clearly distinguishable from the pure respiratory component as such. The respiratory component must be expressed in terms other than BB. Probably the most satisfactory blood value for this purpose is arterial CO_2 pressure (P_{CO_2}) which may be read directly from the Singer-Hastings nomogram [*8*] at the same time BB is determined. This value is usually almost identical with alveolar P_{CO_2} and therefore closely reflects the respiratory disturbance itself. It is of course not expressed in chemical equivalent terms and cannot be used in a manner analogous to BB in many applications of the latter to be mentioned.

Advantages of Buffer Base. The advantage of the buffer base concept in the analysis of acid-base disturbances may be said to start with the fact that the reference system deals with the entire non-respiratory disturbance rather than with its quantitatively insignificant unbuffered fraction. Secondly, a clear-cut quantitative differentiation is made between respiratory and non-respiratory disturbances, a distinction that is fundamental to adequate therapy. It is seldom desirable to try to correct primary respiratory acidosis or alkalosis by administration of alkalinizing or acidifying substances; when possible the respiratory abnormality should be the target of treatment. Thirdly, the quantitation of the total buffer reaction in units of chemical equivalents permits extension of acid-base considerations from terms of concentration alone to terms of absolute amounts, namely, total content of and redistribution within various body fluid phases, and intake and output or the "balance" for the whole body [*10,11*].

In addition to these advantages the buffer base concept provides a convenient framework for interpretation of available data even when it is not possible to determine BB itself. The role of individual ions in the dynamics of acid-base equilibrium is clarified. Strictly speaking, the law of electroneutrality makes it impossible for a change to occur in one ion without an associated change in at least one other ion. Nevertheless it is often convenient to describe the acid-base effect that a certain ionic change would have if

* Singer and Hastings originally used the designation Bb^+ and considered the value to represent primarily the cations equivalent to buffer anions (see the alternate method of deriving the numerical value for BB shown in Figure 1). This cationic excess represents "base" in the traditional clinical terminology. It is equally appropriate, however, to consider the buffer anions, which are proton acceptors and accordingly "base" by the Bronsted terminology. Thus one may consider either the cationic or anionic value as "base" and the other a convenient method of finding a numerically equal value. We prefer not to use a symbol including electrical charge, nor to specify either the cationic or anionic value as primary, since the buffer anion cannot exist without an equal amount of cation. Singer also now uses the simple symbol BB [*9*]. This is also appropriate since buffer reactions involve *pairs* of substances and the term "base" stresses the fact that the desired value is not the total amount of the buffer pair, but only that member which is in the form of base, whether so defined by its buffer anion or by its accompanying fixed cation. The adjective "buffer" is necessary for either terminology, since the remaining cation is "base" (but not buffer base) by traditional clinical terminology, and the remaining anion is "base" (proton acceptor, but not buffer base) by the Bronsted terminology.

[9] SINGER, R. B. Personal communication, 1958.

[10] SINGER, R. B., CLARK, J. K., BARKER, E. S., CROSLEY, A. P., JR. and ELKINTON, J. R. The acute effects in man of rapid intravenous infusion of hypertonic sodium bicarbonate solution. I. Changes in acid-base balance and distribution of the excess buffer base. *Medicine*, 34: 51, 1955.

[11] ELKINTON, J. R., SINGER, R. B., BARKER, E. S. and CLARK, J. K. Effects in man of acute experimental respiratory alkalosis and acidosis on ionic transfers in the total body fluids. *J. Clin. Investigation*, 34: 1671, 1955.

everything else remained the same.* This may easily be done by noting the position of the ion in one of the two equations for calculating buffer base (Fig. 1), and when the associated ionic changes are known, the algebraic effect on buffer base is readily calculated. Furthermore, every

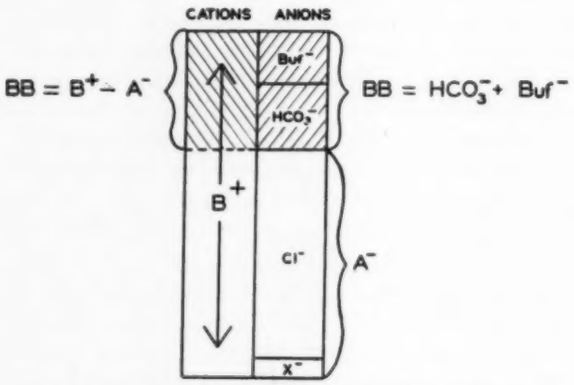


FIG. 1. Diagrammatic representation of buffer base (BB), as modified from SINGER, R. B. and HASTINGS, A. B. [8].

clinician is well aware that transfers of different species of ions produce individual clinical effects which may extend well beyond those on acid-base equilibrium, as for example, salt depletion, edema, potassium intoxication, and others. These problems, not necessarily related to acid-base disturbance, frequently require therapeutic attention. Thus in a condition such as so-called "hypokalemic alkalosis" the need for potassium therapy may occur more readily to the physician who has kept cations under consideration and has not insisted on moving from fixed ion to hydrogen ion each time he thinks of acid-base disturbances.

Finally, it is possible to assess the degree to which other proposed acid-base indices approach the more complete index of buffer base. *Bicarbonate* alone, "alkaline reserve" or "base-bound" bicarbonate, is by far the most frequently used index. In non-respiratory disturbances this index, as well as the total CO_2 content of plasma which approximates bicarbonate concentration, will give a partial reflection of buffer base. Such information is not misleading since the missing component, Buf^-, parallels the change in HCO_3^-. However, in respiratory disturbances Buf^- and HCO_3^- change in *opposite* directions, and the direction of change of HCO_3^- is opposite to that for a similar pH change in a non-respiratory disturbance. Accordingly this index is of somewhat limited value when the disturbance has significant components of both respiratory and non-respiratory nature. *Carbon dioxide combining power* or capacity represents the CO_2 or HCO_3^- content after equilibration of the blood or plasma sample with gas at a "normal" P_{CO_2} (usually 40 mm. Hg). Abnormal values are then considered to represent only "metabolic" disturbance since the respiratory component has been artificially removed. This determination is of limited significance unless the critical equilibration is made in the presence of the important red cell buffers. Even when performed on whole blood the method is less suitable than BB. It does not include the change in Buf^- in a way that will provide a numerical measurement of total buffer change; it does not measure any content actually in the blood, but rather a change from an arbitrary standard; it is easily confused with other methods and as commonly performed does not assure even a reproducible P_{CO_2} equilibration. The method was discontinued many years ago in the laboratory of its origin [12]. Changes in the serum concentration of *sodium and chloride* are used by many clinicians for a rough indication of acid-base disturbance without usually expressing the relation in any numerical value. A convenient index for non-respiratory changes in blood should be the difference in concentration between sodium and chloride, $Na^+ - Cl^-$. This index approximates buffer base only on the assumption that the unmeasured fixed cations or anions have not changed, hence its utility is limited. Nevertheless any of these indices are useful in assessing the total extent and mechanism of acid-base disturb-

* Those who feel uncomfortable assuming even for a moment that any ion changes by itself may note that this assumption is equivalent to assuming that a fixed cationic or anionic change is balanced by a suitable change in buffer anion. If a change in buffer anion is the one under consideration it is assumed to be balanced by a suitable change in fixed cation. These are the assumptions which would attribute to the ionic change under consideration a full effect on BB. If the ionic change was not really associated with an acid-base change the "erroneous" assumptions cancel out in combining "single" terms in a BB expression. In assigning a numerical value to single ionic changes it is recommended that changes in "fixed cation," "fixed anion," or "buffer anion" be described rather than using the expression "base" or "acid." This avoids the conflicting usage that has been applied to the latter terms and also serves as an automatic reminder of which of the two alternate expressions for BB will be affected.

[12] PETERS, J. P. and VAN SLYKE, D. D. Quantitative Clinical Chemistry, vol. 1, 1st ed., p. 935. Interpretations. Baltimore, 1931. Williams & Wilkins Co.

ances if they are combined with comprehension of the physiological processes involved, clinical judgment, and a modicum of common sense.

SUMMARY

It is agreed that acids and bases may be defined in terms of transfers of hydrogen ion. In the body, however, since hydrogen ion changes are almost completely buffered, they cannot be measured adequately as such but only in terms of the accompanying reciprocal change in buffer anions. These are conveniently termed "buffer base" and as proton acceptors may indeed be defined as "base."

The principle of electroneutrality permits this same numerical quantity to be derived as the excess of cations over fixed anions and provides another, and often more convenient, way of determining the same quantity. Changes in each of the factors involved occur simultaneously and are different ways of looking at the same thing. It is not meaningful to try to call any one the "cause" of another. Since the same quantity is determinable as either cation or anion it is most convenient to simply call it buffer "base."

Change in buffer base quantitates a non-respiratory or "metabolic" alteration in acid-base balance. In pure "respiratory" disturbances buffer base does not change, prior to secondary responses. Here, hydrogen ions are redistributed among the buffer anions, i.e., there are reciprocal alterations in the bicarbonate and non-bicarbonate buffer anions. Thus determination of buffer base separates non-respiratory or metabolic and respiratory acid-base disturbances.

Individual ionic effects may be conveniently examined with respect to their effect on buffer base. Although hydrogen ion is the reference point for the entire development (which is consistent with the Bronsted theory), it is convenient to talk directly about effects of other ions rather than to return to the hydrogen ion at every step. We believe it is easier and clearer, once the idea is explained, to say that "an increase of fixed cation over fixed anion is an increase in buffer base" than to say that "an increase in fixed cation over fixed anion is a convenient way to determine an increase in total buffer anions, which in turn is a convenient way to determine a decrease in hydrogen ion." Either is quite acceptable and neither statement leaves the erroneous impression that it is possible to describe a complex situation with a single term or that the pH or hydrogen ion concentration alone adequately describes the disturbance.

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ONE of the essential attributes of the physician must be a readiness to accept the patient's story, and if we should ever cast doubts upon the veracity of his statements the whole structure of clinical medicine would be undermined. On rare occasions, however, it is necessary and proper to view the patient with suspicion, as well as with disbelief, and it is our intention here to point out this exception and to direct attention to a common yet inadequately publicized condition.

For a long time we have been aware in this country of patients who wander from hospital to hospital giving false and often fanciful information concerning their social and medical background, feigning an acute medical or surgical illness, allowing themselves to be subjected to diagnostic and surgical trauma, and who finally disappear after manifesting some form of psychopathic behaviour, usually directed at the nursing staff. Although the majority of doctors had met such a patient, no one had studied them as a group nor written about them in detail until Asher published his paper in 1951 [*1*]. He suggested that the name "Munchausen syndrome" should be used to describe them, explaining that, like Baron Munchausen, these patients have travelled far and, like his stories, their statements although dramatic are mostly false. Despite the fact that he has been challenged on the grounds that this eponym does not reflect the true nature of the famous writer or of his writings [*2*] the name has survived and is now widely used. There are perhaps others, and we would suggest the one included in the title of this paper. However, the exact form that the name takes is less important than the fact that these patients have at last been recognized as a special type of psychopathic personality. They may now be detected more readily and studied more carefully, for knowledge of their existence and the clinical pictures which they may present vastly repays the physician and the hospitals in time and expense saved.

We propose to describe three cases of the syndrome seen in a general hospital.

CASE 1. An obese female railway worker, thirty-eight years of age, was admitted from the casualty department as an emergency at 10:30 P.M. on February 21, 1957. She was reported to have had an attack of loss of consciousness and gave a history of rapidly increasing obesity, decreasing vision for one month, "blackouts" for three weeks, and somnolence, headache, polydipsia and polyuria for about one week. She also described a severe head injury, when sixteen years old, for which an operation with the removal of a blood clot was necessary, and told how she had undergone several laparotomies for "tuberculous peritonitis." Her family history did not seem to be outstanding.

On examination she weighed 234 pounds; she had bilateral frontal burr-holes as well as the scars of many abdominal operations. No obvious mental changes were detected and apart from extensive opaque nerve fibres surrounding each disc, bilateral colombomata of the retina, and grossly constricted visual fields, the nervous system was normal.

A provisional diagnosis of a lesion interfering with hypothalamic functions associated with congenital retinal lesions was made and the appropriate investigations begun. Fortunately she was soon recognized by a physician who had seen her at another hospital and it rapidly became clear that despite the story she had given, her past history was extremely rich in social and medical activities.

After a considerable search it was possible to reconstruct this patient's career and background. Her mother and a brother had each needed psychiatric treatment but details could not be obtained. Her life

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had been uneventful until she left school but thereafter it was crowded with notable episodes. She soon left home and during the space of the next three or four years had two illegitimate pregnancies, two attacks of venereal disease (probably gonorrhoea) and served no less than six prison sentences for theft and prostitution. She moved from place to place and was never able to remain in a job more than a few months. In 1943 she joined the Women's Auxiliary Territorial Service and married but she soon left her home and husband, never to return. A year later she was discharged from the Service and her journeying from hospital to hospital began and has continued up to the present time. Over these thirteen years we have been able to trace thirty-five admissions to thirty general hospitals and thirteen admissions to ten mental hospitals, the majority being in London or towns nearby. It is certain that this is only a small proportion of all her hospital visits but as she uses a number of false names, tracing each of them would be extremely difficult.

When reviewing all the known periods of hospitalization they can be placed in two groups: (1) during the first period (1944 to 1950) she invariably presented in a hospital casualty department with acute abdominal pain, and diagnoses such as "salpingitis," "acute appendicitis," "postappendicectomy adhesions" and "acute abdominal emergency, N.Y.D." were made. She is known to have had at least six laparotomies, with appendectomy and total hysterectomy, but it is possible that additional surgical procedures have also been carried out. After about 1950, however, she stopped complaining of abdominal symptoms and the second phase began: (2) which contains two distinct clinical pictures. First, her admissions to mental hospitals occurred during this period and she was taken to them because of psychopathic behaviour, depression, fear of suicide and other psychiatric states. Having had electroconvulsive therapy with little success, in 1952 a leucotomy (probably the standard type) was performed and it seemed to have some immediate effect. Secondly, concurrently with her stays in mental hospitals and outlasting that phase, were symptoms suggesting a hypothalamic lesion. During the past year she had had at least eight hospital admissions (including the one reported here) because of the symptomatology described already. In each instance extensive investigations have been undertaken but apart from an abnormal electroencephalogram they have all proved to be normal. Our electroencephalogram showed a generalized abnormality consisting of prominent theta activity of moderate amplitude, mostly precentrally, at 5 to 6 cycles per second and runs of regular and irregular waves on a background of normal alpha rhythm. It was thought that the record was compatible with a deeply placed lesion near the third ventricle and more than five years ago (before the leucotomy) a similar recording was made.

Psychometric studies were carried out by Dr. T. Grygier who with Drs. J. Barker and I. Collie is studying the psychologic and psychiatric aspects of the Munchausen syndrome [*3*]. He found our patient to be a person who, although of average intelligence and lacking in psychotic traits, was extremely egocentric, emotionally immature, narcissistic, exhibitionistic and who lacked insight into her motives and behaviour. He succinctly described her as presenting "a picture full of conflict and tension."

During the patient's stay in this hospital, a letter appeared in the *Lancet* [*4*] describing her and mentioning some of her peregrinations. Another letter two weeks later [*5*] told of the same woman who had arrived at a hospital casualty department at midnight with the same clinical picture. She had in fact been discharged from our care only a few hours previously.

Comment: The information which this patient gave us was almost entirely false yet it was remarkable how plausibly she presented it. At no time during her stay did she present any psychopathic behaviour and although she appeared to have little or no insight into her case the majority of her statements were clever fabrications, aided no doubt by her experience of medical matters gained during numerous contacts with hospital staffs. Nevertheless, there were abnormal electrical findings which have not yet been explained; like the obesity they antedated the leucotomy so that neither can be regarded as sequelae of this procedure, although the blackouts, if genuine, may be. Nor is the electroencephalogram like the abnormal patterns seen in psychopaths [*6*]. It is true that the possibility of a hypothalamic lesion has not been entirely ruled out in this case, but it seems very unlikely. It is also correct to assume that some of her admissions to mental hospitals may have been genuine in view of her known mental instability. It cannot be denied, however, that her behaviour on the whole has been most unusual.

This patient's psychopathy is familial for, as well as her mother and father, her eighteen year old son cannot keep a job and has recently appeared in court charged with homosexual practices.

Case II. An obese woman who gave her age as thirty-six years was admitted as an emergency case at 10 o'clock on a Saturday evening (July 23, 1955).

She had suffered earache and discharge for three days and blurring of vision, headache and stiffness of the neck for twenty-four hours. On admission to a surgical ward she was said to have vomited and had become suddenly unconscious with marked neck

retraction. The aural discharge was thought to be due to otitis externa, but in view of her level of consciousness and hypotonia of the left limbs a left cerebellar abscess was considered. In the first place an exploratory mastoidectomy was carried out but all structures reached were normal. Following this procedure she began to improve and twelve hours later was only drowsy; left-sided weakness and sensory disturbance could now be demonstrated. At this stage a functional component was suspected.

Cerebrospinal fluid was normal in all respects, as was an electroencephalogram and other investigations. An x-ray of the skull, however, revealed bilateral, posterior parietal burr-holes and she now admitted that she had been in another hospital ten years previously. The records concerning this hospitalization indicated that she had suffered a purulent meningitis but the responsible organism had not been discovered. Because of left-sided signs a ventriculogram to rule out a brain abscess had been performed. She had recovered after appropriate treatment for the meningitis but left-sided signs persisted.

Gradually she improved and as she did so it became clear that many of her symptoms were either grossly exaggerated or actually feigned. The left-sided weakness and slight reflex changes however persisted and she had a constant pyrexia, occasionally a temperature reading of 104°F. being made. In view of our suspicions, many attempts to check the thermometer readings were made, but under close observation and sampling at various sites an elevation was always recorded; however she had none of the usual accompaniments of hyperpyrexia.

One day her belongings were searched and besides a number of broken thermometers her case record from another hospital was found. It now became clear that this woman had visited many hospitals, in each of them presenting the same problem and often staying for months. She usually appeared as an acute cerebral emergency which she would survive and then after weeks of observation and investigations for "pyrexia of uncertain origin" she would be handed over to the psychiatrists, one of whom described her thus: "gross hysterical release phenomena with pathological lying in a brain damaged woman of previously hysterical personality." In their treatment, however, they were as unsuccessful as the physicians who had preceded them or as the surgeons who first tackled the problem.

After this exposure she was transferred to another ward where her temperature fell to normal and soon thereafter she walked out of the hospital without consent and has never been seen or heard of since.

Comment: Like our first patient, this woman had abnormal central nervous system signs resulting, on this occasion, from an acute purulent meningitis. The feature that was never explained, however, was her ability to produce a high temperature despite all the usual precautions of the nursing and medical staff.

CASE III. At 11:30 P.M. on June 17, 1957, a man was brought to the Casualty Department and admitted to the hospital. He had been found lying in the street in a semi-conscious state and when examined could give only a very fragmentary history. Apparently he was an Irish steeplejack who had suffered "blackouts" for three years; he gave his age as forty years. Examination was limited but showed that he had bilateral, posterior-parietal burr-holes, a left upper quadrantanopsia which was probably homonymous, a partial left lower motor neurone facial palsy, weakness of the right limbs with diminished reflexes and sensation on that side.

A number of bizarre opisthotonic attacks in which he did not lose consciousness were witnessed and he was given anticonvulsants. The next morning he was more rational and a more detailed examination confirmed the finding of the night before.

The cerebrospinal fluid pressure and the contents were normal. X-rays of the skull showed the burr holes but were otherwise normal. Two electroencephalograms (ten days apart) were also normal.

As the sedation was reduced, he became more rational and spoke vaguely of a head injury and of having been in several hospitals in the Midlands, but he was unable to remember their names or when he was in them. It was concluded that the abnormal neurological signs had resulted from the old cranial trauma and that there had been no recent change, but requests to various hospitals for information concerning this patient were fruitless. After three weeks in the hospital and having had no further attacks, he discharged himself.

Three days later telephone calls from another hospital confirmed our suspicions that we had been dealing with a case of Munchausen's syndrome. It transpired that the patient was known to the police as a frequent hospital visitor.

Comment: This man entered the hospital at a time when we were well aware of the Munchausen syndrome but even so it was a considerable time before we realized that we were dealing with another example. It is, of course, possible that he was suffering from post-traumatic epilepsy and that a postictal state necessitated his admission. The peculiar attacks, the normal electroencephalogram and the final unravelling of the case, however, weigh against this conclusion. As in Cases I and II, there were organic neurological signs and evidence of previous cranial surgery. Unfortunately it was impossible either to trace past hospitalizations or to discover the exact nature of the original cranial injury. His pretraumatic personality

was also unknown and it could be suggested that his peregrinations were due to an acquired organic brain disorder. It seems unlikely, however, that such a patient would receive the type of notoriety which the police accorded him.

COMMENTS

The three cases reported are typical examples of the syndrome described by Asher [*1*]. No doubt others have occurred previously in the literature but they would be difficult to find and even if discovered it is unlikely that they would add much to what is known already. Recently a condition in some ways resembling it has been described in fictitious form in a newspaper article [*7*].

Judging from personal experience and the correspondence evoked by the papers of Asher [*1*] and Gawn and Kaufmann [*8*], the condition is a common one. Eighteen letters followed the original article [*1*], and in addition to giving further information concerning the travels of Asher's three patients, authors described an additional thirteen; most hospital doctors have seen three or four. They seem to be more common in large cities, especially London, where they can visit many hospitals with less expenditure of energy and with less risk of being recognized than in a smaller town. They do, however, travel far, sometimes with alarming rapidity, and at least one British patient has extended his activities to the Continent [*8*]; the patient referred to here is probably the most travelled example of Munchausen's syndrome, for there are many reports of him [*9*] and he has visited our hospital at least once. Their geographical distribution is of interest but little is known of it at the moment; they occur in Sweden [*2b*], however, and are known as "Kopenickiades," after the German town of Kopenick in which a famous hoax took place in 1906. The type of health facilities offered to the public in various countries is clearly an important factor; it may be that the Munchausen syndrome is a product of the welfare state and its free health service. It would be of great interest to know whether or not these patients are found in countries in which free hospitalization is less readily available. If they are not, another evil of a state system of medicine becomes apparent.

The patient, who can be male or female (despite our cases it seems to be more common amongst men), invariably turns up at a hospital casualty department as an acute emergency. He usually appears late at night or during the weekend and it has been suggested that he selects the time when the younger and less experienced casualty officers are more likely to be on duty [*10*]. It is unknown for him to have a doctor's letter introducing his problem, and he is usually accompanied by a passer-by or a workmate. His clinical manifestations are varied but Asher [*11*] has suggested a classification according to the main presenting features and he has supplied a striking and appropriate nomenclature. Thus there is (1) the patient with acute abdominal symptoms, *laparotomophilia migrans*, (2) the patient with bleeding from a bodily orifice, *haemorrhagica histrionica*, and (3) the patient with acute neurological features such as coma, "blackouts" and headaches, *neurologica diabolica*. Our patients were examples of the third type but it is of note that an individual may have belonged to more than one group; initially Case I was in the first group and later in the third. Whether there is any correlation between the basic personality defect and the type of symptomatology, or whether the latter is determined by the person's cunning or by his knowledge of medical matters, is not known.

As well as the florid and convincing history, which may however arouse mild suspicions because of variability and inconsistency, and physical manifestations which are cunningly produced, there may be true organic signs in addition [*1*]. They are usually congenital or of a chronic nature and they help to trap the unwary and make a complex clinical picture even more perplexing. Our patients each had these features; congenital retinal lesions in Case I, minimal neurological signs of long-standing in Case II, and neurological sequelae of brain trauma in Case III. In Case I the ocular findings had at one time or another helped to produce diagnoses of malignant hypertension, intracranial neoplasm, pituitary tumour and tuberculous choroiditis. The patient of Davis [*12*] had transposition of the viscera. It is however possible that a few patients have a true organic illness in addition to their hobo behaviour. Thus Davidson [*13*] described a patient with myocardial infarction and auricular fibrillation as well as pathological peregrinations. These cases deserve separate consideration, however, for whereas the typical Munchausen patient is never in need of general hospital treatment these

patients may require it. That they exist should be realized but as they are difficult to handle it is fortunate that they are less common than those without acute organic disease.

There is still much that is unknown concerning the Munchausen syndrome but the psychiatric and psychologic aspects are the most pertinent. Investigations are proceeding [*3*] and it is clear that the vast majority of, if not all, patients are severe psychopaths [*14*] who indulge in grotesque and purposeless falsehoods (pseudologia fantastica), pathological lying, restless vagrancy, fraudulence, deception, masochism, petty pilfering and purposeful hoaxing. Their behaviour at times may be very similar to, or identical with, malingering and effortless lying is always a prominent feature. In fact they seem able to deceive themselves by their own fabrications which can be differentiated from the confabulations of Korsakov's psychosis by their skillful and well organized construction. It is known that pseudologia fantastica may occur in organic states such as hypoglycemia produced by an islet cell tumour of the pancreas, or general paralysis of the insane [*15*], but there was no evidence of these conditions in our patients nor were they present in the cases taken from the literature. Our patients had each suffered a brain injury but it could not be said that this was the cause for their psychopathic behaviour, which in Case I antedated the trauma. Furthermore their activities were entirely in keeping with those of the patients who had no evidence of previous brain involvement.

Their motives for behaving in this extraordinary fashion have not been established with certainty, but Asher [*1*] has suggested some of the possible explanations. As far as our patients were concerned, none seemed to be using their hospitalization as a convenient method of receiving drugs, nor were they wishing to avoid the police or any unpleasant consequences of previous misconduct. The third patient was in fact known to the police as a hospital vagrant. It has been suggested that some patients might have a grudge against hospital staffs and so enjoy deceiving them, but this does not seem to be a prominent factor. It is possible that our patients enjoyed the attention and the confusion which they skillfully created and, being pathological liars, they presumably derived considerable satisfaction when surrounded by a receptive audience; there was never any outward expression of such pleasure however. The cunning method some patients use to produce hyperpyrexia by manipulation of the thermometer (Case II), bleeding by self-inflicted minor trauma (haemorrhagica histrionica) and periorbital oedema by the subcutaneous injection of an irritant (another case observed in this hospital), indicate an intent to deceive but it is rarely clear how they hope to profit. Some patients no doubt frequent hospitals for the shelter and nutrition provided and there may in this respect be a seasonal incidence; our first patient seemed to indulge in hospital migrations more often during the winter months. Some financial reward is also possible during hospitalization either by pilfering or by collecting for non-existent lotteries (Case I); Birch [*16*] points out that the possession of hospital-marked garments may be a useful diagnostic sign. Nevertheless, whilst accepting the advantages of admission to hospital they must also be prepared to tolerate the inquisitiveness of the interne and the knife of the surgeon, to which they expose themselves. Some who will not submit to the latter take their own discharge, but regarding the others, doubtless the trauma inflicted satisfies masochistic traits. No doubt several etiological factors may operate in any one case but further study will show the relative importance of each, or the presence of others unrecorded here.

Treatment is clearly determined by the underlying psychiatric defect but, as with most psychopathic persons, it would be expected to have limited value. The leucotomy and electroconvulsive therapy in Case I may have relieved the depression and suicidal tendencies but it has not influenced the patient's peripatetic activities. It is nevertheless important to realize that although patients with the Munchausen syndrome are capable of producing considerable annoyance and inconvenience and may closely simulate malingerers, they are nevertheless sick people.

If treatment is likely to be unrewarding, it is necessary to consider the possible prophylactic measures which may protect us from this not inconsiderable band of hoaxers. The best method would be to circulate a photograph of the culprit to the casualty department of each hospital in the town in which he is known to operate, but this may not be within our legal rights. Furthermore these patients are curiously intolerant to photography and will rarely allow such exposure; the patient in Case I, however, submitted. A descriptive "rogues gallery" containing clear

descriptions of examples of the syndrome similarly located or in a central office would be of almost equal value [*17*], and certain London hospitals have their "Munchausen lists" [*16*]. The publication of all cases in the medical press, originally encouraged by Asher [*1*], is also useful and, as demonstrated by the *Lancet* correspondence concerning our Case I, it may bear fruit; the casualty officers at another hospital having read the report of Heathfield [*4*] recognized the patient and, as usually happens, she departed when it was clear that deception was no longer profitable or possible. Similarly the publication by Gawn and Kaufmann [*8*] helped Jones [*18*] and others to identify one of the most troublesome examples of the condition. Another patient was the subject of seven letters in the *Lancet* during the early part of 1956 and those who summarized his case history were no doubt helped by previous correspondence.

These patients are likely to remain a common problem, however, because, like a hobo who has earned a bad reputation in one district, the patient with the Munchausen syndrome will go to an unsuspecting and therefore more advantageous area. Thus at one stage in her career our first patient went to Liverpool where only a small part of her activities has been revealed to us. A suggestion made by Birch [*16*] may help, for a while at least, to deal with this tendency; if the patient is told that he has the Munchausen syndrome and if he announces this at the next hospital, he will be detected at once. As with hoboes and other nomads, however, a secret system of communication between them may exist and news of the nomenclature would soon spread.

Possibly our best defense against these persons is to be aware of their existence and to include the Munchausen syndrome in the differential diagnosis whenever a bizarre and insoluble clinical problem, which seems slightly improbable and which arouses faint suspicion, occurs in a much-travelled psychopath with multiple operation scars. It seems clear, however, that the best method of handling the proved and incorrigible patient has not yet been determined.

Above all, our clinical scepticism must be reserved for only these patients and we must never feel resentful if they humiliate us by successfully belittling our diagnostic prowess. As illustrated by our Case III, despite our awareness of the condition, sooner or later most of us will be deceived.

SUMMARY

Three examples of a syndrome originally popularized by Asher [*1*] and linked by him with the name of Baron Munchausen are described. The typical patient presents at a hospital as an acute emergency and usually has a lurid yet plausible medical and social history, which is later found to be entirely false and fabricated. There may be organic signs, which are either congenital or of long-standing, but they help to emphasize the validity of the clinical picture. After fruitless investigations with or without surgical operations, a diagnosis cannot be made and the patient eventually discharges himself and goes to another hospital where the process is repeated. The psychiatric and psychological aspects are of interest but so far little is known of them, except that all the patients are psychopaths. Treatment and prophylactic measures are discussed and it is to be emphasized that rapid recognition of the syndrome will produce handsome dividends in time and expense saved.

ADDENDUM

Since this paper was completed, our first patient has been reported again (*Lancet*, 2: 1006, 1957; *Lancet*, 2: 1069, 1957) and Chapman (CHAPMAN, J. S. Peregrinating problem patients —Munchausen's syndrome. *J. A. M. A.*, 165: 927–933, 1957) has described American cases. Additional British cases (WRIGHT, A. D. How patients have deceived me. *Hunterian Soc. Tr.*, 14: 13–30, 1955–1956) should also be noted.

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The Barrel Deformity of the Chest, the Senile Lung and Obstructive Pulmonary Emphysema*

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THE condition commonly known as senile or postural emphysema has not been reviewed in detail since 1934 [*1*]. Methods now available permit an evaluation of pulmonary function which was not then possible. Moreover, understanding of the disturbed physiology of obstructive pulmonary emphysema, and other common pulmonary diseases, has vastly improved. It seemed important to study the physiological basis of senile emphysema.

A characteristic feature of senile emphysema is said to be the barrel deformity of the chest. It has been suggested, but not proved, that the barrel chest exerts harmful effects on the lungs. The large rounded thorax has been suspected of sufficiently stretching the lungs to rupture the alveolar septae. Kountz and Alexander [*1*] concluded that senile emphysema primarily involved the chest wall and not the lung. The purpose here is to report the results of a study specifically designed to determine the relationship between the barrel deformity of the chest and its associated pulmonary physiology.

HISTORICAL NOTE

The classic description by Laennec [*2*] divided pulmonary emphysema into two types, vesicular and interlobular. He described vesicular emphysema as consisting of dilatation of the air cells which he thought was produced by chronic obstruction to the outflow of air. Interlobular emphysema, on the other hand, consisted of interstitial collections of air within the lungs, which followed violent paroxysms of coughing.

The vesicular emphysema of Laennec clearly corresponds to what is commonly known today as obstructive emphysema. Laennec also described the condition of the lungs in aged persons. He applied no special term to this, but discussed it in a section on the structure of the lungs. His rare ability for accurate observation is demonstrated by the following passage on the senile lung [*3*].

"This black matter is not found in the lungs of young children. In adults and elderly persons it is more or less abundant; while in very old subjects it perhaps is found in less quantity. In the last named class of persons the lungs present some other remarkable characters: the calibre of all their vessels seems diminished; they become in some sort exsanguine: the partitions of the air cells thinner than natural, on which account their substance, rendered more rare, becomes less elastic, and thus yielding to the atmospheric pressure on the opening of the body, they are found to occupy not more than one-third of the cavity of the pleura."

It is of interest that Laennec's report also contained a description of pulmonary atrophy [*4*]. He used this term to indicate a small, contracted (and apparently fibrotic) lung situated in a thoracic cavity which previously had been the site of empyema.

An early suggestion of the term "senile emphysema" is contained in Rokitansky's Manual of Pathological Anatomy published in 1842 [*5*]. In a section entitled "Pulmonary atrophy (atrophia senilis)," Rokitansky points out that this condition is a pathological one. He describes the air cells as dilated. At this point, the word emphysematous appears in brackets. Rokitansky noted that the walls of the chest "sink down upon the atrophied lungs, become flattened laterally, and take on a conical form." He thus described the barrel deformity of the chest which Laennec had already described as occurring in some patients with vesicular pulmonary emphysema.

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A source of confusion in attempting to determine the origin of the term "senile emphysema" was the view expressed by Gairdner [*6*] that atrophy of the lung always accompanied pulmonary emphysema. Unlike Rokitansky, however, Gairdner made no special reference to senile atrophy as separate from pulmonary emphysema. Waters [*7*] published extensive studies on pulmonary emphysema in 1860, but made no mention of a senile type. In 1864, Concato [*8*] published a lucid article entitled "Senile Emphysema, Diffuse Bronchial Catarrh, Catarrhal Pneumonia." It appears that senile emphysema held no special connotation for him, because the case which he described was a ninety year old woman who had emphysema, pneumonia and distended neck veins. He attempted no clear distinction between senile and obstructive emphysema.

Jenner [*9*] appears to have originated the terms "large lunged and small lunged" emphysema in 1871. His concept is confusing, however, because he described patients with small lunged emphysema as past middle life, and as having shortness of breath on exertion and diminution in the size of the thorax. He stated that certain patients with atrophous (small lunged) emphysema had extreme dilatation of the air cells. It would seem that like Rokitansky, he considered the condition a pathologic one. Contrary to Rokitansky's view, however, he thought that all chest diameters were reduced. Jenner did point out that small lunged emphysema was less devastating to the patient than its large lunged counterpart. He also described two other types of "pulmonary vesicular" emphysema.

Reference to senile emphysema has not been encountered in the American literature before 1880 when Flint [*10*] published a clinical lecture in the Philadelphia Medical Times. He wrote (of senile emphysema) "The size of the chest instead of being increased, may be notably diminished. The resonance on percussion may be diminished." In 1893, Osler [*11*] published a section on "atrophic emphysema" in his text. His reluctance to accept this as a disease entity is evident by the comment: "It is really a primary atrophy of the lung coming on in advanced life, and scarcely constitutes a special affection." Further, he stated that the size of the chest was small in these "withered-looking old persons." Osler, then appears to have agreed with Flint in partially following the concept of small lunged emphysema proposed by Jenner.

It seems likely that the term senile emphysema evolved gradually from the older vagaries, pulmonary atrophy and atrophia senilis. Unquestionably, there has been a wide variation in the meaning of these terms. Symptoms of dyspnea and cough were deemed important by some authors and not important by others. Deformity of the chest has also been an inconstant feature in the descriptions of senile emphysema. Kountz and Alexander's extensive review [*1*] served to perpetuate the term on the basis, of what was then, a plausible theory. They considered the barrel deformity of the chest as characteristic of senile emphysema. This view is still prevalent.

SUBJECTS

GROUP I. *Emphysema group:* These subjects were selected because they were considered from routine clinical evaluation to have obstructive pulmonary emphysema. All had moderate or severe dyspnea. Frequently, this was accompanied by cough and sputum production. Care was taken to avoid patients with typical bronchial asthma. Physiological studies revealed changes considered characteristic of pulmonary emphysema in every instance. More than half of these subjects also had elevations of arterial carbon dioxide tension. Age was not a consideration for selection in this group.

GROUP II. *Barrel chest group:* These subjects were required to be sixty-five years of age or older, and present a marked barrel deformity of the chest (a ratio of anteroposterior to lateral diameter of 0.9 or more). In general, they did not have symptoms of pulmonary disease. One subject had dyspnea and a cough which was productive of scanty amounts of sputum. Three other subjects had mild cough in the morning associated with very scanty sputum production. None of the other subjects had any symptoms of pulmonary disease. All subjects in this group were considered to have increased resonance on percussion of the chest. All were ambulatory.

GROUP III. *Unseleced group:* These subjects were required to be sixty-five years of age or older, and were studied as a control group for comparison with the aged subjects in group II. During the period from July 15, 1956 to November 15, 1956, all white men admitted for prostatic resection were studied. The attending surgeon controlled admissions without altering his routine policies for providing patient care. Four subjects are not included as they failed to complete all procedures. The reasons are: one died, one was psychotic and disoriented, and two refused to cooperate fully. Every effort was made to complete all studies prior to operation. This was accomplished in eleven cases. In the four others, procedures were

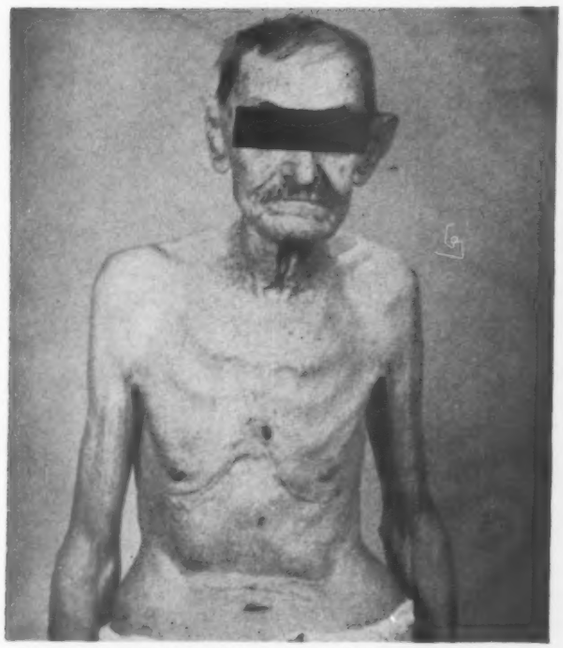


FIG. 1A. Front view of subject 6 in group II showing the typical barrel deformity of the chest.

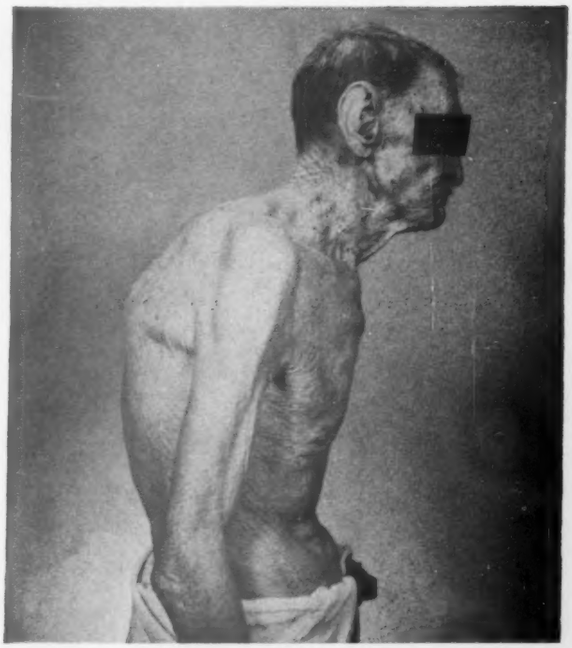


FIG. 1B. Side view, same subject, showing typical barrel deformity of chest.

not undertaken until five, ten, fourteen and thirty-one days postoperatively when the subjects had regained strength. At the time the studies were made, all subjects were ambulatory. An analysis of the elastic properties of the lungs in this group of subjects already has been published [*12*]. In general, these subjects did not have major symptoms of pulmonary disease. The clinical details and individual lung volume measurements are found in that report.

GROUP IV. *Healthy young group:* This group was composed of young house officers and medical students who had no evidence of pulmonary or other disease on clinical history or physical examination.

METHODS

Measurements of the chest were performed as follows. With the subject standing erect, a metal tape was passed about the chest and held in a horizontal position at the level of the fourth costo-sternal junction. Pelvimetric calipers were then used to measure the anteroposterior and lateral dimensions of the chest at this level. All measurements were made at pulmonary mid capacity, and at maximum inspiration and maximum expiration. Repeated measurements agreed to within 0.5 cm. for the diameters, 1 cm. for the circumference. All spirometric measurements, residual volume determinations and maximal breathing capacities were performed in the sitting position. Methods used for these measurements as well as for the determinations of arterial hemoglobin oxygen saturation, arterial carbon dioxide tension, static and functional pulmonary compliance and airway resistance were performed as described in the previous publication [*12*].

RESULTS

Configuration of the Chest. The best single expression of the barrel chest deformity is the anteroposterior to lateral thoracic ratio. This was termed the chest index by Hurtado and associates [*13*]. Figure 1 is a photograph of subject 6 in group II showing the typical barrel deformity of the chest. Mean values for the thoracic ratio were slightly larger (0.03 to 0.07) when computed from the position of maximal inspiration than from the position of maximal expiration. The frequency distribution of the maximal inspiratory thoracic ratios for all four groups are presented in Figure 2. The mean values were: group I, 0.88; group II, 1.04; group III; 0.86; and group IV, 0.73.

Figure 3 presents the relationship between age and the anteroposterior to lateral thoracic ratio in all subjects. In group III, there were four subjects in whom the AP/lateral ratio was greater than 0.9. The two subjects with most marked rounding of the chest were considerably older than the group average. That the configuration of the chest does not correlate with the ratio of residual volume to total lung capacity is evident in Figure 4.

Excursion of the Chest. The mean values for the maximal change in chest circumference between inspiration and expiration were 4.3 cm. for group I, 5.5 cm. for group II, 5.2 cm. for group III and 7.2 cm. for group IV. The frequency distribution of these values is presented in Figure

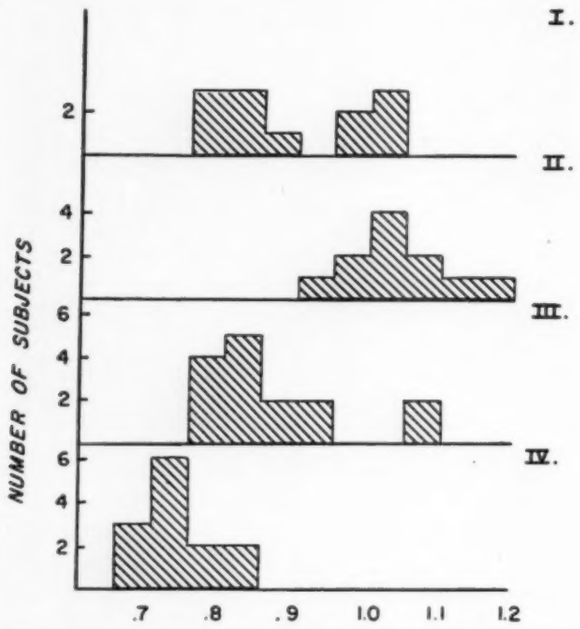


FIG. 2. The frequency distribution of the ratio of antero-posterior to lateral thoracic diameters. From above downward, the figures illustrate emphysema, group I; aged barrel chest, group II; aged unselected, group III; and healthy young, group IV.

5. One should note particularly the overlap between the various groups. Gilson and Hugh-Jones [*14*] reported similar findings in a larger number of subjects. This only serves to point out the futility of measuring the circumferential expansion of the chest to obtain information about lung function.

Lung Volumes. Individual measurements of the subjects in group II are presented in Table I. The mean values for each group are presented in Table II. The mean total lung capacity was slightly lower in group I than in the other groups. There is close agreement between the mean total lung capacities of groups II, III and IV. Norris and associates [*15*] found that the total lung capacity does not change with aging. The values which they obtained for total lung capacity in elderly groups were less than those obtained in young groups, but the differences were not significant when correction was made for the smaller size of their elderly subjects. This contradicts the findings of Robinson [*16*], but the data of Greifenstein and associates [*17*], Needham and co-workers [*18*], and the present study all support such a conclusion.

The mean vital capacity was reduced to 2.7 L. in group I. It is similar in groups II and III, 3.8 and 3.6 L., respectively, but notably higher, 5.4 L., in group IV. The severe reduction in vital capacity was anticipated in group I because of the presence of emphysema. That the vital capacity decreases with advancing age has been known since 1846 when Hutchinson [*19*] introduced the clinical spirometer. Values for vital capacity reported by several previous authors who studied elderly subjects are compared with the present series in Table III [*20*]. When allowances are made for body size, and for the position of the subjects during the measurements, the remaining differences are seen to be small. The values of Norris and co-workers are the smallest reported and yet the body surface area of their subjects was only slightly smaller than those of Greifenstein and associates. Incomplete cooperation by the subjects could produce this type of discrepancy.

The mean residual volumes in the aged subjects of this report are only slightly larger than in the group studied by Needham and co-workers [*18*]. Interestingly enough, their subjects were also studied in the sitting position and had a mean ratio of residual volume to total lung capacity almost identical with that found in the present groups II and III. When allowance is made for differences in age and in position during study, the remaining discrepancies between the present aged subjects and those previously reported are seen to be small. (Table III.)

Other Physiologic Studies. The mean index of intrapulmonary gas distribution was markedly abnormal in group I, at 7.6 per cent. It was almost identical in groups II and III, at 1.7 and 1.9 per cent, respectively, and it was significantly less in group IV, at 0.6 per cent. The higher alveolar nitrogen after oxygen breathing in the aged subjects confirms the results of Greifenstein and associates. These authors reported studies with a more sensitive single breath technic as suggested by Fowler and co-workers [*21*], as well as with the present method. They concluded that aged subjects have a slightly abnormal intrapulmonary distribution of inspired gas.

The mean maximum breathing capacity was 32 L./minute in group I, 60 L./minute in groups

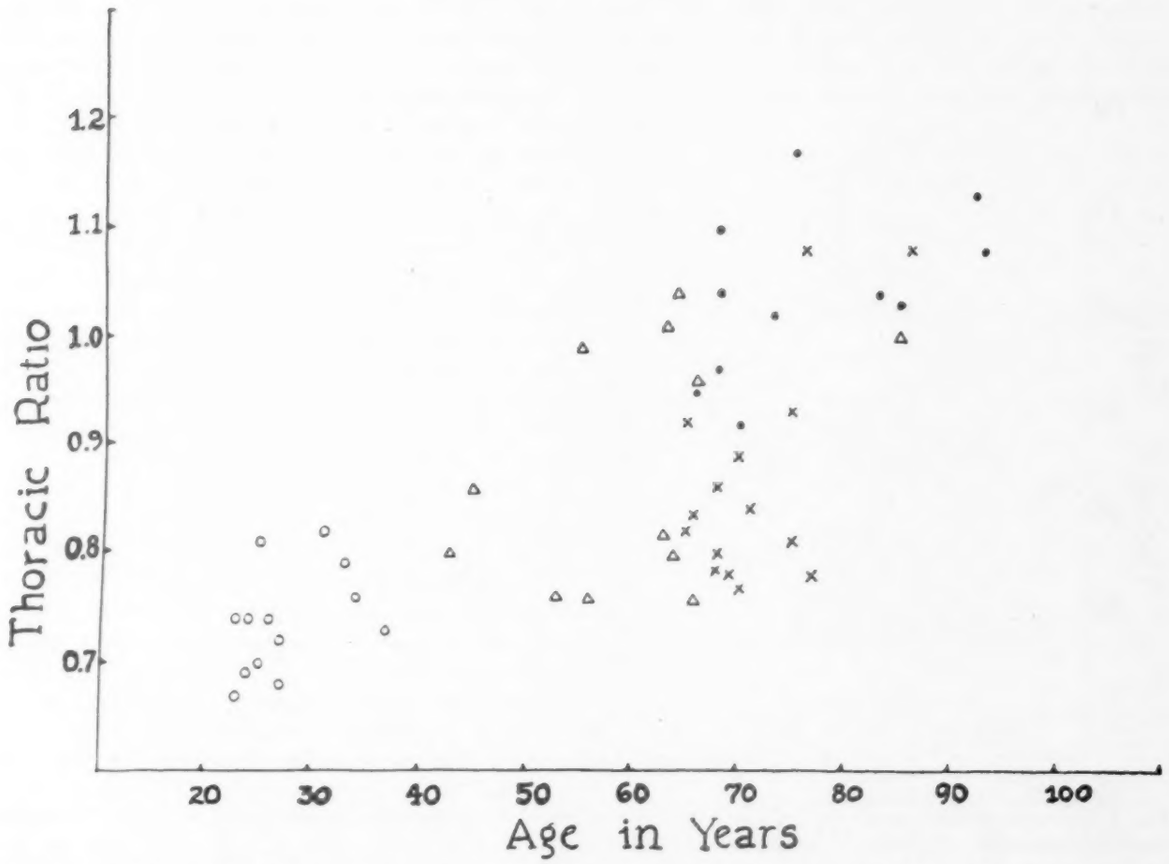


FIG. 3. Scattergram relating the ratio of anteroposterior to lateral thoracic diameters to age. The symbols are: group I, triangle; group II, black dot; group III, x; and group IV, open circles.

II and III, and 130 L./minute in group IV. The findings in these aged subjects agree with those of Greifenstein [*17*], Needham [*18*], and Norris [*15*]. In any event, the maximum breathing capacity in old age is fairly well preserved.

The mean arterial hemoglobin oxygen saturation was low in group I, and closely similar in groups II and III. The values for the latter two groups were 93.4 per cent and 94.3 per cent, respectively. These figures are similar to those found by Greifenstein. The mean arterial carbon dioxide tension was 53 mm. Hg for group I, and 36 mm. Hg and 37 mm. Hg, respectively for groups II and III.

COMMENTS

Aged persons have a smaller vital capacity, a larger residual volume, and a larger functional residual capacity than young persons. Minor irregularities occur in the intrapulmonary distribution of inspired gas in the aged. The maximum breathing capacity is reduced, but not severely enough to limit physical activity. The enlargement of the residual volume and reduction in vital capacity is associated with an alteration in the elastic properties of the lung [*12*]. Intrathoracic pressure is less negative at mid-capacity in elderly than in young subjects, although the volume of air in the lungs is greater in the aged. The pressure volume diagram of the lungs is curvilinear over its entire range, differing from the relatively linear pressure volume diagram of young subjects. Airway resistance is normal, permitting a rapid rate of expiratory air flow, and hence a relatively well preserved maximum breathing capacity.

Patients with obstructive pulmonary emphysema have similar, although more marked changes in the lung compartments including diminished vital capacity, enlarged residual volume, and increased functional residual capacity. The pressure volume diagram of the lungs is similar to that seen in aged subjects. On the other hand, the intrapulmonary distribu-

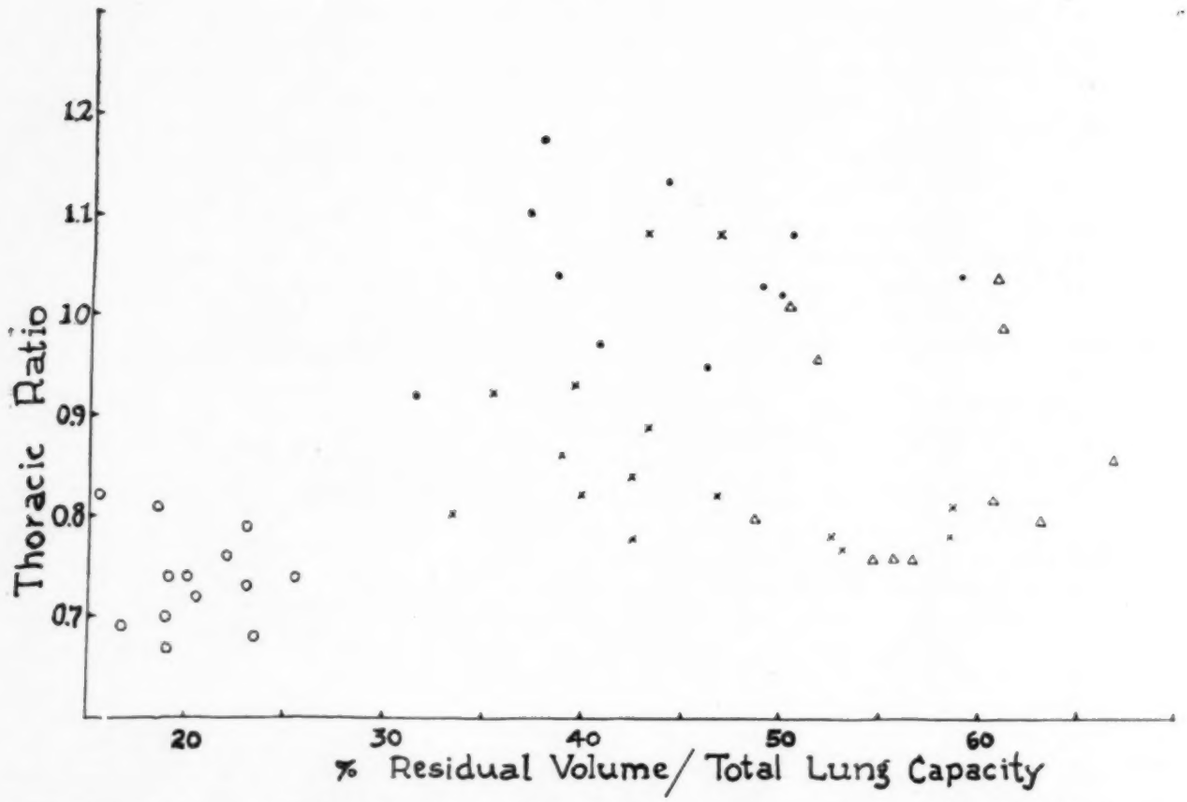


FIG. 4. Scattergram relating the ratio of anteroposterior to lateral thoracic diameters to the ratio of residual volume to total lung capacity. The symbols are the same as in Figure 3.

tion of inspired gas tends to be markedly abnormal, and the maximum breathing capacity severely reduced. Perhaps the most striking difference between aged subjects and patients with obstructive emphysema occurs in airway resistance which is markedly increased in emphysema. A marked reduction in the maximal rate of expired air flow occurs, and hence, a severe diminution in the maximum breathing capacity.

The barrel deformity of the chest is characterized by dorsal kyphosis, prominence of the sternum, and an increased ratio of anteroposterior to lateral chest diameters. The upper three or four intercostal spaces are widened and the ribs are more oblique than usual. The mechanism which predisposes patients with obstructive pulmonary emphysema to this type of chest deformity is not entirely clear. Such patients have an increased amount of intrathoracic gas. This is evident from the finding of an increased functional residual capacity. The sizable quantity of trapped gas reported in such patients by Bedell and co-workers [*22*] also attests this over-inflation. The present finding of only a slight increase in the ratio of anteroposterior to lateral chest diameters with the change from maximal expiration to maximal inspiration suggests that over-inflation does not entirely explain the development of the barrel chest deformity in subjects with pulmonary emphysema. It seems likely that the impaired ventilatory mechanics contribute in some manner to produce the observed changes in the positions of the ribs and the contour of the thoracic spine. Why this change does not occur uniformly in all patients with obstructive pulmonary emphysema is not known.

It is apparent that a marked barrel deformity of the chest may occur incident to skeletal alterations alone. Kountz and Alexander found a straightening of the thoracic spine could elevate the sternum. They also observed marked abnormalities of the intervertebral discs in patients with advanced dorsal kyphosis who had a barrel deformity of the chest. It is of interest that rounding of the thoracic cage occurs with advanced age in the general population [*23*].

Aged subjects are seen to exhibit three phe-

nomena pertinent to this discussion. First, obstructive pulmonary emphysema may appear from whatever cause. This may be recognized by the presence of markedly increased resistance to expiratory air flow and a distinct abnormality in the intrapulmonary distribution of inspired gas. Second, the elastic properties of the lungs are so altered with age as to permit greater inflation with less negative intrathoracic pressure. This change occurs in a majority of older persons and is not accompanied by any increase in airway resistance. Finally, the typical barrel deformity of the chest may occur independently of any change in the lungs, or it may appear in association with emphysema.

In aged subjects, there is no difference in the lung compartments, total lung capacity, maximum breathing capacity, indices of intrapulmonary mixing or arterial blood gases whether the barrel deformity of the chest is present or not. Moreover, measurements of static and functional pulmonary compliance and of airway resistance in selected aged subjects from the present group with barrel deformity of the chest were in no way different from those already reported in unselected aged subjects [*12*].

Kountz and Alexander did not present any evidence that the barrel deformity of the chest produced physiologic changes in the lungs although this has been implied from their report. They clearly demonstrated that some patients with the barrel deformity and hyperresonance to percussion of the chest had more nearly normal pulmonary function (as evidenced by vital capacity, arterial hemoglobin oxygen saturation,

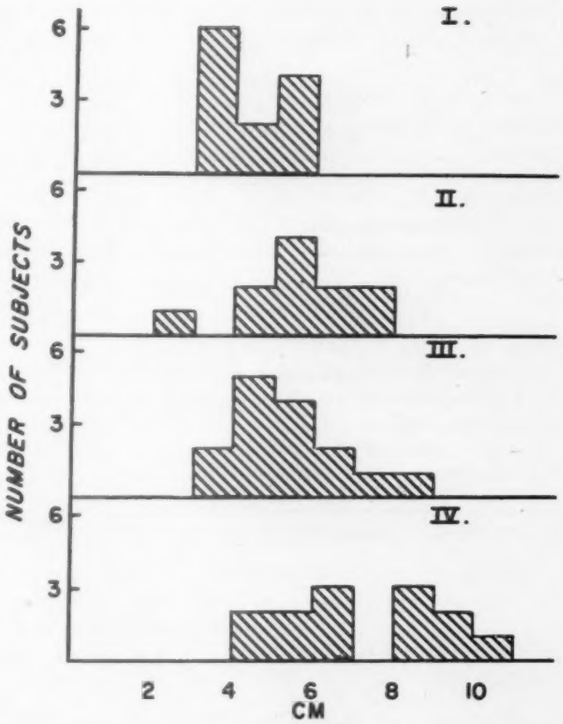


FIG. 5. The frequency distribution of the maximal circumferential excursion of the chest.

TABLE I

PHYSICAL CHARACTERISTICS AND PHYSIOLOGICAL MEASUREMENTS IN SUBJECTS WITH THE BARREL CHEST IN GROUP II

Subject No.	Age (yr.)	Height (cm.)	Body Surface Area (sq. m.)	Total Lung Capacity (ml.)	Vital Capacity (ml.)	Ratio RV/TLC (%)	Functional Residual Capacity (ml.)	Index of Mixing (%)	Maximum Breathing Capacity (L./min.)	Arterial pCO_2 (mm. Hg)	Arterial Oxygen Saturation (%)
1	68	174	1.85	6856	4299	37.3	4910	5.120	52.9	39	85.6
2	70	183	1.99	8022	5493	31.5	4528	0.369	104.4	51	91.0
3	75	175	1.76	7640	4744	37.9	4604	2.831	73.2	40	91.0
4	68	177	1.56	6532	2662	59.2	5073	2.257	53.4	32	96.1
5	68	185	1.98	9293	5502	40.8	6317	1.729	81.7	46	93.7
6	93	172	1.61	6512	3227	50.4	4490	1.315	51.4	30	92.7
7	85	160	1.58	5270	2689	49.0	3650	1.763	41.9	39	95.3
8	92	170	1.87	4134	2313	44.0	2561	0.727	44.1	29	93.7
9	83	165	1.64	4380	2691	38.6	2671	0.914	67.5	28	95.1
10	66	177	1.97	8279	4457	46.2	5533	1.351	53.9	37	96.1
11	73	163	1.54	6604	3317	49.8	4718	0.716	39.7	29	97.2

TABLE II
MEAN VALUES

Data	Group I Emphysema	Group II Barrel Chest	Group III Unselected	Group IV Healthy Young
Number of subjects	12	11	15	13
Age (yr.)	60 (11)*	76 (10)	71 (6)	28 (5)
Height (cm.)	172 (7)	173 (8)	172 (5)	178 (4)
Weight (kg.)	60 (11)	64 (12)	64 (9)	71 (7)
Body surface area (sq. m.)	1.70 (0.13)	1.76 (0.18)	1.76 (0.12)	1.88 (0.11)
Total lung capacity (ml.)	6280 (718)	6684 (1611)	6582 (859)	6768 (863)
Vital capacity (ml.)	2724 (466)	3763 (1177)	3598 (600)	5368 (593)
Functional residual capacity (ml.)	4771 (616)	4460 (1128)	4636 (838)	3781 (598)
Ratio RV/TLC (%)	56.5 (6.2)	44.2 (7.8)	45.1 (7.9)	20.5 (3.0)
Index of mixing (% N.)	7.612 (2.225)	1.736 (1.336)	1.887 (1.425)	0.565 (0.421)
Maximum breathing capacity (L./min.)	31.9 (14.0)	60.4 (19.7)	60.1 (24.6)	130.0 (17.3)
Arterial hemoglobin oxygen saturation (%)	85.4 (6.2)	93.4 (3.1)	94.3 (2.1)	.....
pCO_2 (mm. Hg)	53 (13)	36 (8)	37 (4)	.....
Thoracic ratio (AP/Lat. diam.)	0.88 (0.11)	1.04 (0.08)	0.86 (0.10)	0.73 (0.05)
Circumferential chest excursion (cm.)	4.3 (0.9)	5.5 (1.4)	5.2 (1.4)	7.2 (2.3)

* Numbers in parentheses are standard deviations.

TABLE III
LUNG VOLUMES IN ELDERLY MEN

Author	Year	No. of Subjects	Mean Age (yr.)	Body Surface Area (sq. m.)	Total Lung Capacity (L.)	Vital Capacity (L.)	Residual Volume (L.)	Ratio RV/TLC (%)	Position during Study
Kaltreider, Fray and Hyde	1938	8	64	....	5.01	3.43	1.58	31.5	Recumbent
Robinson	1938	7	62	1.82	5.77	4.05	1.72	29.8	Recumbent
Robinson	1938	5	77	1.79	5.12	3.20	1.92	37.5	Recumbent
Greifenstein, King, Latch and Comroe	1952	11	61.5	1.74	5.92	3.48	2.43	40.9	Semi-recumbent
Needham, Rogan and McDonald	1954	10	64	1.79	5.97	3.27	2.70	44.9	Sitting
Norris, Shock, Landowne and Falzone	1956	20	65*	1.72	4.76	2.80	1.95	41.0	Recumbent
Norris, Shock, Landowne and Falzone	1956	20	75*	1.71	4.81	2.37	2.44	50.7	Recumbent
Norris, Shock, Landowne and Falzone	1956	20	85*	1.65	4.66	2.36	2.30	49.4	Recumbent
Present study Group II	1957	11	76	1.76	6.68	3.76	2.92	44.1	Sitting
Present study Group III	1957	15	71	1.76	6.58	3.60	2.98	45.1	Sitting

* Mean age not given, groups ranged 60 to 69, 70 to 79 and 80 to 89 years.

and arterial carbon dioxide tension) than patients with obstructive pulmonary emphysema. They failed to show whether or not such subjects differed from normal subjects. It has been suggested that obliquity of the ribs in the barrel deformity of the chest might impair function of the muscles of respiration. This question was investigated using a technic similar to that described by Rahn, Otis, Chadwick and Fenn [*24*]. Although maximal intrathoracic pressure is somewhat less in aged emphysematous subjects and in aged subjects with the barrel deformity of the chest than in healthy young subjects, it is clear that this factor does not impose a primary limitation in any sense. The observed intrathoracic pressures were far in excess of any which might conceivably be required for pulmonary ventilation. More recently, it has been suggested that stiffening or loss of elasticity of the thoracic cage might explain an inability of patients with "non-obstructive emphysema" to expire to a normal level of residual volume [*22*]. Measurements of chest expansion and of residual volume in the present series are not compatible with such a contention since in neither instance could any difference be demonstrated between aged subjects with a marked barrel deformity of the chest and unselected aged subjects.

It is concluded that the three phenomena described above will explain the observed changes in the chest and the lungs of aged persons. If any condition such as senile, postural or non-obstructive emphysema exists as an entity, it will apparently require definition by methods other than those used in the present study. It seems reasonable, as suggested by Greifenstein, to discard the term senile emphysema.

SUMMARY

1. A study has been made of the physiological basis of senile emphysema.

2. Measurements of the chest and physiological studies of lung function were carried out in a group of aged subjects who had a marked barrel deformity of the chest. Similar studies were performed in a group of subjects with obstructive pulmonary emphysema, in an unselected group of aged subjects and in a group of healthy young subjects.

3. Comparison of the mean values for total lung capacity, functional residual capacity, residual volume, intrapulmonary distribution of inspired gas, maximum breathing capacity, arterial hemoglobin oxygen saturation and arterial carbon dioxide tension failed to reveal any significant difference between the group of aged subjects with a marked barrel deformity of the chest and the unselected aged subjects. Additional studies were discussed which also have failed to disclose changes characteristic of those subjects with the barrel deformity of the chest.

4. It was concluded that physiological evidence for any condition such as senile, postural or non-obstructive emphysema is lacking.

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Pulmonary Compliance in Granulomatous Disease of the Lung*

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PULMONARY function studies [*1–11*] in patients with granulomatous diseases of the lung have been mainly concerned with ventilation, lung volumes and the respiratory gaseous exchange. In some instances it has been shown that the roentgenographic findings cannot be correlated with these disturbances of function [*9,11,12*]. Some of these studies [*3,4*] have demonstrated also the difficulty of relating the clinical and pathologic findings to the functional laboratory determinations. The moderately reduced values of the usual pulmonary function tests in themselves have not completely shown the malfunction. Stone [*13*] suggested study of the physical properties of the lungs in assessing the pulmonary elastic function in cases of fibrosis. In a study of patients with heart disease, Saxton [*14*] attempted a relationship between vital capacity and the compliance as an index of the loss of elastic tissue. The purpose of this study was to derive information on the elastic behavior of the lung in granulomatous disease of the lung. With the exception of four patients (having miliary tuberculosis, plasma cell granuloma and silicosis) the entire group of patients were considered to have pulmonary sarcoidosis. Measurements of the elastic behavior of the lungs have been compared to the clinical status of the patients and to measurements of their lung volumes.

METHOD OF STUDY

Pulmonary compliance is the expression which relates changes in lung volume to changes in transpulmonary pressure. It gives information of the elastic behavior of the lung. It is expressed mathematically:

$$\text{Pulmonary compliance} = \frac{\Delta \text{ volume in liters}}{\Delta \text{ pressure in cm. } H_2O}$$

All measurements were made from the end expiratory relaxation volume (functional residual capacity) and during inspiration over a volume range of 750 ml. to 1,000 ml. while the patient was seated. Over this range, compliance is approximately a straight line relationship.

This technic has been described in previous reports [*15–17,27*]. Inspiration was interrupted stepwise every 250 ml. by an electrically controlled solenoid valve. During the periods of no air flow the differences between intrapulmonary and intraesophageal pressures were measured with a transducer and recorded [*17*] after amplification on a direct-writing oscillograph. When the corresponding volume and pressure changes are plotted on a graph, the slope of a line drawn through these points indicates the compliance of the lungs.

Lung volumes were also measured while the patients were seated and are expressed at BTPS. For the vital capacity the largest volume was recorded after two to three successive efforts. The functional residual capacity was measured with the closed circuit helium method [*18*]. The total lung capacity (BTPS) was determined from the functional residual capacity and the inspiratory capacity. The regression equations of Baldwin et al. [*19*] were used to estimate predicted values for vital capacity.

MATERIAL

Twenty-nine patients hospitalized with pulmonary granulomatosis were studied. The diagnosis was made from clinical, laboratory (including biopsy) and characteristic roentgenographic findings [*20–26*]. In most instances roentgenographic study disclosed a diffuse miliary type of lesion; in two instances only hilar and paratracheal enlargement of lymph nodes were evident. In eight of the patients serial pulmonary function studies were performed. Seven patients were studied before and after cortisone therapy. One patient (15) was restudied after three years. The ages of the patients varied from sixteen to fifty-nine years; their mean age was 33.7 years (standard deviation ±

* From the Department of Medicine, State University of New York, Downstate Medical Center, Brooklyn, New York. These studies were aided by a contract between the Office of Naval Research, Department of the Navy and State University of New York.

TABLE I

ANTHROPOMETRIC AND PULMONARY FUNCTION DATA

Patient No.	Sex and Age (yr.)	Height (cm.)	Weight (kg.)	Body Surface Area (M^2*)	Vital Capacity (L.)	Expiratory Reserve (L.)	Residual Volume (L.)	Functional Residual Capacity (L.)	Total Lung Volume (L.)	Lung Compliance ($\Delta V/\Delta P$ L./cm. H_2O)	Pulmonary End Exp. Pressure (cm. H_2O)	Arterial PaO_2 (mm. Hg)	Arterial $PaCO_2$ (mm. Hg)
1	M, 24	181	66	1.85	(4.51)†	(1.58)	(1.13)		(5.63)				
					2.43	1.08	1.77	2.85	4.19	.07	.....	60	32
2	F, 23	163	64	1.68	(3.19)	(1.12)	(.80)		(3.99)				
					2.68	.98	.80	1.78	3.48	.07	.....	...	..
3	F, 19	177	64	1.79	(3.51)	(1.23)	(.88)		(4.39)				
					3.17	1.20	1.33	2.53	4.50	.10	.....	...	..
4	M, 46‡	162	60	1.64	(3.60)	(1.26)	(1.10)		(4.70)				
					2.49	.31	1.75	2.05	4.30	.08	−4.5	...	..
					2.64	1.19	1.66	2.85		.08	.....	...	..
5	M, 26	176	58	1.71	(4.32)	(1.51)	(1.08)		(5.40)				
					1.95	.66	1.39	2.05		.05	−8.3	64	39
	2 weeks after cortisone				2.93	1.15	.98	2.13	3.91	.12	.....	...	..
6	F, 21	164	56	1.60	(3.12)	(1.09)	(.78)		(3.90)				
					0.62	.25	1.77	2.02	2.39	.03	−9.2	...	..
	2 weeks after cortisone therapy				0.91	.41	1.94	2.36	2.85	.04	.....	...	..
	5 months after interrupted cortisone therapy				1.56	.86	.85	1.71	2.41	.06	.....	...	..
7	F, 31	160	89	1.92	(3.01)	(1.05)	(.75)		(3.76)				
					1.32	.60	.35	0.95	1.66	.06	−3.5	103	33
8	M, 59‡	160	..	1.78	(3.16)	(0.79)	(0.94)		(4.89)				
					2.40	0.26	2.67	2.93	5.07	.12	.....	78	38
9	F, 38	159	66	1.74	(2.86)	(1.00)	(.87)		(3.74)				
					1.69	.27	1.91	2.18	3.60	.08	.....	85	30
	4 weeks after cortisone therapy				2.53	.91	.89	1.80	3.42	.20	.....	86	38
10	F, 30	160	60	1.62	(3.01)	(1.05)	(.75)		(3.76)				
					2.83	1.14	1.05	2.19	3.88	.22	0	75	39
11	M, 16	166	47	1.50	(4.28)	(1.50)	(1.07)		(5.35)				
					2.54	.36	.45	0.81	2.97	.06	.....	68	36
12	M, 39	180	86	1.92	(4.22)	(1.48)	(1.28)		(5.50)				
	2 weeks after cortisone therapy				2.51	.63	1.81	2.44	4.32	.06	−8.0	83	37
13	F, 21	168	68	1.77	(3.22)	(1.13)	(.80)		(4.02)				
					2.64	.71	.32	1.76	3.47	.08	.....	87	34
14	M, 31§	171	67	1.87	(4.28)	(1.46)	(.87)		(5.37)				
					3.26	.44	1.07	1.86	4.37	.06	.....	80	23
	4 weeks after cortisone therapy				4.04			2.56	4.68	.07	.....	90	35
15	M, 47	160	66	1.68	(3.59)	(1.30)	(1.10)		(5.18)				
					1.88	.45	1.30	1.74	3.17	.06	.....	71	41
	During 3 weeks cortisone therapy				3.01	0.49	0.83	1.32	3.83	.11	.....	...	..
16	M, 25	177	91	2.08	(4.36)	(1.53)	(1.09)		(5.45)				
					2.94	.88	.68	1.58	3.74	.07	.....	62	39
					1.56	.31	1.14	1.45	2.74	.03	.....	80	40
	During 4 weeks cortisone therapy				3.26	.75	1.46	1.21	4.72	.09	.....	86	39
17	F, 35	159	60	1.60	(2.93)	(1.02)	(.73)		(3.66)				
					1.64	.50	1.39	1.89	3.03	.06	−4.0	85	36
18	F, 39	157	52	1.50	(2.74)	(.96)	(.84)		(3.58)				
					1.44	.66	.84	1.50	2.29	.06	−2.5	...	..
19	F, 23	166	60	1.68	(3.22)								
					1.77	0.49	0.89	1.32	3.45	.04	−7.0	81	37
	During cortisone therapy				2.67	0.53	0.79	1.26	3.45	.05	.....	91	33
20	M, 22	172	65	1.77	(4.33)	(1.52)	(1.08)		(5.42)				
					3.46	1.58	.68	2.25	4.14	.13	.....	66	39
	Later serial study				2.77	1.18	.92	2.10	3.68	.08	−5.0	81	25
	During 6 months cortisone therapy				3.53	1.70	.96	2.67	4.50	.08	.....	86	40
21	F, 31	175	98	2.10	(3.18)	(1.11)	(.80)		(3.98)				
					3.12	0.55	1.16	1.71	4.28	.22	−2.0	...	..
22	M, 24	173	64	1.75	(4.31)								
					2.90	.....	.....	.....	.....	.05	−3.5	67	45
23	M, 22	178	..	1.97					(4.35)				
					2.27	0.48	1.35	1.83	3.26	.06	.....	82	43
24	M, 49	163	51	1.53	(3.62)	(1.27)	(1.05)		(4.66)				
					2.22	.89	.56	1.45	2.87	.02	−6.0	71	44
25	F, 48	171	60	1.70	(2.91)	(1.02)	(.89)		(3.80)				
					1.93	.91	1.11	2.10	3.06	.06	−5.0	93	48
26	F, 24	160	48	1.48	(3.10)	(1.09)	(.78)		(3.88)				
					1.90	.64	.95	1.59	2.85	.04	−7.2	95	50
27	M, 23¶	185	..	1.88	(4.20)	(1.05)	(1.15)		(5.85)				
					5.29	1.15	1.16	2.30	6.45	.16	.....	...	..
28	F, 24	173	..	1.81	2.32	.....	.....	.....	.....	.06	.....	...	..
29	M, 20	180	..	1.83					(5.21)				
					2.71	0.83	1.46	2.29	4.17	.12	.....	75	40

* Body surface area calculated from Dubois Height-Weight Formula: Area = $Wt.^{0.425} \times Ht.^{0.725} \times 71.84$.
† Numerals in parenthesis are predicted values.
‡ These patients had silicosis.
§ This patient had a plasma cell granuloma of the lung.
¶ This patient had miliary tuberculosis.

11.1). Comparison was made with data on healthy subjects.

RESULTS

Bearing on the Method. The limitations of the method have been well described in other reports [*16,26–31*]. Duplicate studies in these patients within a day or two gave a standard error of ±.005 L. per cm. H_2O.

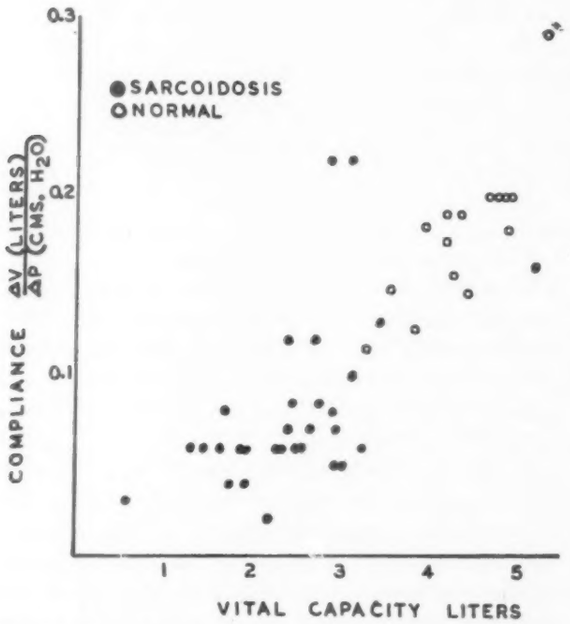


FIG. 1. The plot of vital capacity and the compliance values show a significant relation between vital capacity and compliance. The lower the vital capacity, the lower the pulmonary compliance. The open circles are the findings for normal subjects and the closed circles represent the patients with pulmonary granulomatosis.

Clinical Data. The age, height, weight and estimated body surface area of each patient are listed in Table I.

The mean value for the compliance of the twenty-nine patients was 0.08 with a range from .02 to 0.22 (S.D. ± .04). (Table I.) The compliance values were not related to the degree of abnormality noted on the chest roentgenogram. Compliance values tended to be lower in those patients with more severe degrees of dyspnea. Patients 10, 21 and 29 had no symptoms at the time of study; (their respective compliance values were .22, .22 and .12 cm. H_2O/L.). These three patients were studied because of abnormal characteristic chest roentgenograms.

Vital Capacity and Total Lung Capacity. The compliance values were significantly related to the vital capacity; in general, a positive relation was found. (Fig. 1.) The vital capacity was normal to low as judged from the predicted value, the mean value being 2.45 L. (S.D. ± .89), a reduced value. In all patients studied there was also a reduction of the total lung capacity which was also positively related to the reduced compliance values. (Table I.) The mean total lung capacity was 3.67 L. (S.D. ± .96), a reduced value for a comparable group of normal subjects.

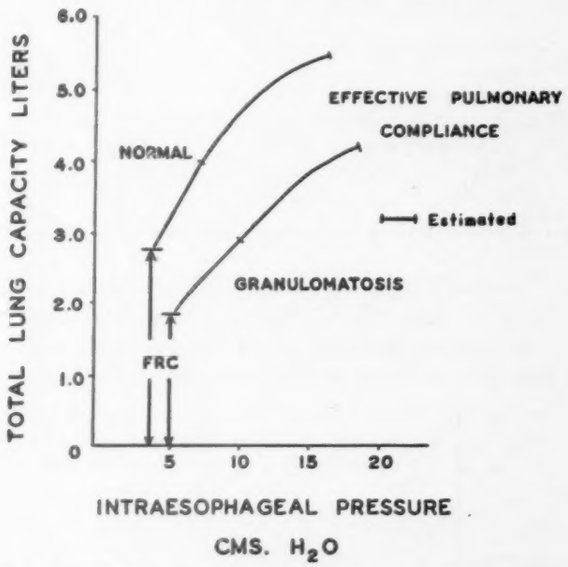


FIG. 2. This is the average plot of the compliance curve of patients with granulomatous lung disease and a comparable group of normal subjects. The functional residual capacity and the total lung capacity of the patients are reduced. The slope of the compliance curve for the patients is flatter.

Functional Residual Capacity and Residual Volume. The functional residual capacities were normal to low (1,889 L., S.D. ± .49 L.). The reduced functional residual capacity was found with a low compliance value. An average plot of functional residual capacity and compliance of a comparable group of patients was made. (Fig. 2.)

The slope of the curve in patients differs from the normal. The end expiratory transpulmonary pressure level is greater than in the normal but this is so variable a measurement that no conclusions can be drawn. (Table II.) The average end expiratory pressure for fifteen of the patients studied was −5.3 cm. H_2O, S.D. ± 2.1 cm. H_2O. For a comparable group of normal subjects it was found to be −4.1 cm. H_2O, S.D. ± 1.4 cm. H_2O. The difference is not significant.

TABLE II

MEAN DATA FOR NORMAL SUBJECTS AND PATIENTS

	Mean Age (yr.)	Mean Height (cm.)	Mean Functional Residual Capacity (L.)	Mean Compliance ($\Delta V/\Delta P$/L./cm. H_2O)	Mean Pulmonary End Expiratory Pressure (cm. H_2O)
Normal subjects (15).....	27	167	2.77	0.154	−4.10
6 males		(S.D. ± 7)	(S.D. ± 0.32)	(S.D. ± 0.02)	(S.D. ± 1.4)
9 females					
Patients with granulomatous pulmonary disease (15)	32	166	1.73	0.08	−5.31
		(S.D. ± 8)	(S.D. ± .451)	(S.D. ± 0.44)	(S.D. ± 2.1)
6 males					
9 females					

Arterial Oxygen and Carbon Dioxide Tensions. If 38 to 40 mm. Hg is used as the normal range, only four of the patients with low compliance had a carbon dioxide tension within the normal range. The average arterial carbon dioxide tension was 38 mm. Hg, range 23 to 50 mm. (S.D. ± 6.0). There is no relation noted with compliance. The arterial oxygen tensions are all, except for those of two patients, below the normal value of 95 mm. Hg, range 93 to 102. The average arterial oxygen tension was 77 mm. Hg, range 60 to 103 (S.D. ± 11.5) in the patients studied. This is a significant reduction and, except for four of the patients, is associated with decreased pulmonary compliance.

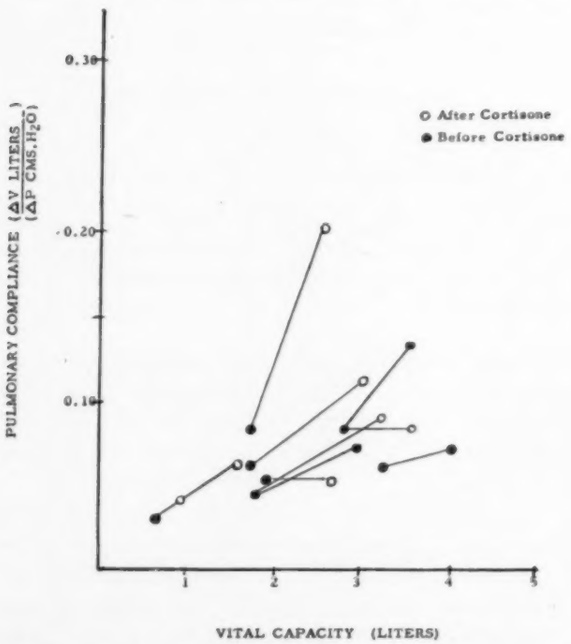


FIG. 3. The changes of the initial values for vital capacity and pulmonary compliance are plotted before and after cortisone therapy. It will be noted that some patients had values which became reduced before the administration of cortisone but improved after cortisone therapy. Other patients showed no appreciable improvement after cortisone therapy.

Cortisone. Only seven patients were studied for the effect of cortisone therapy. After the initiation of cortisone therapy an improvement in compliance and vital capacity occurred in four of the patients. There was also an increase in arterial oxygen tensions. (Fig. 3.) The early improvement in these three separate measurements was unassociated with any appreciable roentgenographic changes. Even though the chest roentgenograms in these patients remained unchanged, there was definite amelioration of symptoms, dyspnea being characteristically reduced. Usually when the chest roentgenogram eventually became normal, the compliance values followed suit and were then usually approaching the normal range. Patients 6 and 20, however, failed to have any improvement in pulmonary compliance even after six months of cortisone therapy.

COMMENTS

The patients as a group had reduced pulmonary compliance while at rest. It is known that healthy subjects show a wide range of values, but even after allowances for differences in height, all measurements in these patients were below the normal limits* [*28,29*]. (Fig. 4.) Three patients (10, 21 and 29) were exceptions having a pulmonary compliance within normal limits. None of these patients had symptoms at

* Predicted compliance = 0.00343 (Ht.) − 0.425 ± 0.035 liters/cm. H_2O.

the time of study, although their chest roentgenograms had the characteristic abnormalities of pulmonary sarcoidosis. Another patient (20), who at the time of the initial study was found to have a normal value for pulmonary compliance and was also without symptoms, showed a reduction of compliance two weeks later on a repeat study, and cough and dyspnea were present at this time. (Fig. 3.) Four of seven patients who were studied during cortisone therapy showed improvement in the compliance measurement; later this was followed by regression of the disease as noted by the gradual disappearance of symptoms and clearing of the chest roentgenograms.

The compliance of the lung is an index of the elastic recoil of the lung. The method of measurement gives compliance values which are influenced by factors other than the elasticity of lung tissues. The lung size is a major factor, and total lung capacity is appreciably reduced in this group of patients. Certain qualitative, and perhaps quantitative, changes of the elastic elements of the lung will also reduce compliance. The pathological alterations of the granulomatous process can produce these effects. The various conditions which may have influenced the measurements are considered.

The Relation of the Subdivisions of Total Lung Capacity. There is a close relationship between the decrease in the vital capacity and the reduction in compliance. (Fig. 1.) The vital capacity as well as the total lung capacity are indexes of the effective size of the lungs. This close relationship of vital capacity and compliance can be explained on this basis, as other studies have shown [*14,35*]. Both vital capacity and compliance may be reduced because of the loss of elastic properties of the lung. Vital capacity may, however, be affected by weakness, fatigue, reduced chest cage mobility or an incomplete effort, and may by itself be a misleading measurement. Compliance under such circumstances may not necessarily change. Although sarcoidosis may involve the voluntary muscles [*36*], this factor was not overtly present in any of the patients in this study.

Measurements of pulmonary compliance made at the functional residual capacity in the range of tidal volume are a limited expression of the volume-pressure relationships. It has been shown that the volume-pressure relationship changes at different lung volumes and with change in the functional residual capacity. In Figure 2 the average values for compliance, intraesophageal pressure at the end of a normal expiration and the total lung capacity (all measured with the patients in the sitting position) among fifteen patients have been compared with fifteen normal subjects of similar bodily

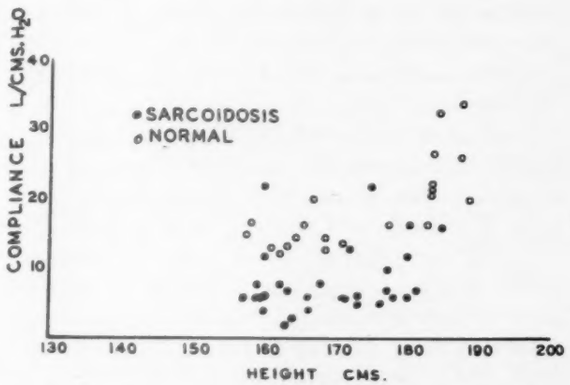


FIG. 4. The pulmonary compliance when plotted against the height shows no relation for the patients, but does show a positive relation for normal subjects.

characteristics and age. The intraesophageal pressure at the maximum inspiratory volume is an estimated value.

The decrease in functional residual capacity appears associated with an increased esophageal pressure at end-expiratory level, and results in a flatter curve of compliance in the range of tidal volume. The compliance of the patients is decreased as a result of this change in the volume-pressure relationship. Although this slope of the compliance in the patients reflects the stiffened lungs resulting from loss of elastic properties of the lung, factors other than the reduction of the functional residual capacity may play a role. In normal subjects, when inspiration is started from levels approaching the residual volume of the lungs, a lag of inspiratory volume change to the applied transpulmonary pressure change occurs (hysteresis) [*35*]. This lag may explain in part the reduced compliance.

The Number of Elastic Units of Ventilation. The reduction of the total lung capacity may be explained as partial or complete collapse of the alveoli. In granulomatosis of the lung such collapse may be brought about by the actual involvement of the walls of the alveoli by the pathologic process [*20*]. Alveolar gas may thus be completely replaced or a partial collapse from the process may occur. Lesions also are common in the peribronchial, perivascular and subpleural

areas so that large nodules may compress air. Changes in the airways by edema or bronchial secretions may also lead to alveolar collapse. A part or all of these abnormalities was present in the patients.

When the stiffer granulomatous sections of the lung are separated by relatively normal portions, most of the lung movements probably occur in the more normal areas of the lung.

Surface tension is important for consideration. The air-liquid interface in the alveolar units, as well as other surface tension changes in the tissue elastic units, requires a greater pressure for distention than a lung with a liquid-liquid interface. The force of surface tension may further enhance the obstruction of small bronchioles. If this factor is widespread it will cause a significant number of respiratory units to be closed and a smaller lung volume to be obtained on inflation. The measured compliance will be reduced. The granulomatous inflammatory process may exaggerate the normal air interface and in this way reduce the functional alveolar units. The elastic properties of the lung thus can be influenced by both of these factors. The reduction of the total lung capacity may be a reflection of these factors [*35*]. However, the absence of intra-alveolar exudate as found by Longcope tends to incriminate other causes of increased surface tension [*20*].

In addition to these factors, reduction in the quantity of elastic units participating in ventilation from partial or complete airway obstruction may likewise play a role. Edema and bronchial mucosal involvement by the granulomatous infiltrates, and mediastinal compression from the lymph node enlargement are factors present in the patients, all of which may cause partial or complete bronchial obstruction. However, the usual functional tests to demonstrate airway obstruction, i.e., the maximum breathing capacity, maximum expiratory flow rate, maximum inspiratory flow rate, timed vital capacity (1 second) failed to show obstruction to airflow. The results of these tests were moderate reduction to normal values as were noted by McClement et al. [*41*]. Compliance values on the other hand, may be abnormal before these conventional functional tests show impairment [*34*]. Otis and his associates [*30*] have shown that when there is unequal resistance in different portions of the lung and unequal distribution of gas, compliance will vary with the frequency of breathing. The compliance decreases with increased frequency of breathing. Although this factor may contribute to the decrease in compliance of the patients, the method used for study recorded during interrupted breathing when conditions were static. This effect was not a part of the measurements.

The Quality of the Elastic Units of Ventilation. Structural changes in the lungs will directly affect its elastic characteristics. The epithelioid tubercles of sarcoidosis are most numerous in the alveolar walls, with peribronchial areas often obliterating the alveolar capillaries. This interstitial localization must account for the rigidity of the lungs in the patients. It would appear that most of the patients had findings of an alveolar capillary block syndrome as characterized by the decreased arterial oxygen tensions and decreased carbon dioxide values. There is in the granulomatous process a deposition of collagen in the interstitial tissue of the lung. This substance has a modulus of elasticity 400 times that of the elastic fibers and their limit of extension is only a small fraction greater than their resting length [*37*]. Only a small number of these collagen fibers (in relation to the number of elastic fibers) need be present to reduce the compliance of the lung as a whole [*38*]. Because these collagen fibers are formed in a mesh, the modulus of elasticity is far less than that of isolated fibers. It is this deposition which is the major factor in producing the rigidity of the lungs. There is considerable variation in the extent, localization and nature of sarcoid lesions, which may account for the physiologic variations.

Disturbances in the blood gas relationships found in the lung are associated with increased rigidity of the lungs. Infiltrations in the alveolar walls may cause impairment of diffusion and an increased venous admixture [*2,5*]. Arterial oxygen tension and carbon dioxide tensions are both lowered in most of the patients. Hyperventilation was present in all. Dyspnea was a prominent clinical symptom except in the three patients with normal compliance values.

Pulmonary function tests may guide the need for steroid therapy. James [*12*] uses only radiologic evidence and symptoms as a basis for treating patients with these agents. The presence, nature and severity of functional impairment cannot be predicted from roentgenologic changes in the lung. Definite improvement in the compliance values is found for most patients in this study treated with the steroids. The other modalities of pulmonary function improve and

the symptoms decrease. However, not every patient treated with cortisone shows this improvement. Cortisone may affect not only the structural changes in the lung, but also some of the other factors discussed which are not non-reversible stress-strain characteristics of tissue elements. However, quantitative as well as qualitative variations of the sarcoid lesions may influence the result with cortisone. No observations have been presented on the long range effect and the duration of the improvement in terms of years, except for one patient. Patient 15 initially was found to have a compliance value of .06 L./cm. H_2O; subsequent to cortisone therapy for four weeks the compliance value increased to 0.12 L./cm. H_2O. The chest roentgenogram was normal and all symptoms had abated. A study three years later showed a compliance value of .08 L./cm. H_2O, with an obstructive breathing pattern by other pulmonary function tests. The arterial oxygen saturation was found to be 86 per cent. It was 96 per cent at the time of the study immediately following the cortisone therapy. This study is not concerned with the late effects of this disease but this example is mentioned to indicate what may be found later in some patients. Longer follow-up studies are needed to evaluate critically the prognosis and natural history of pulmonary granulomatosis.

SUMMARY AND CONCLUSIONS

Pulmonary compliance was measured in twenty-nine patients with pulmonary granulomatosis. All measurements were made with the patients in the sitting position and from end-expiratory resting volume by the interrupted technic. The mean compliance value was .080 L./cm. H_2O (S.D. $\pm$ .04) which is significantly lower than that in healthy subjects.

The lowered compliance value was related to a reduced vital capacity and total lung capacity. Associated with the reduced compliance was a reduction in arterial oxygen tension in all but four patients.

The pulmonary compliance determination appears to be a measurement of considerable value for the evaluation of the effect of granulomatosis on the elastic properties of the lung. Cortisone therapy appears to be effective in enabling some patients to regain normal stress-strain characteristics of pulmonary tissue elements. In other patients the change in the elastic properties is non-reversible. The rigidity of the lungs, as found by the method of study, appears to be due in the main to changes of elasticity in the interstitial tissue of the lung.

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The Rapid Diagnosis of Ventilatory Failure with the Carbon Dioxide Analyzer*

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VENTILATORY failure is commonly present with many diseases, but it is often overlooked because it is difficult to diagnose by symptoms or physical examination.

It is the purpose of this paper to emphasize the need for accurate appraisal of the patient's ventilatory status and to present a method by which this appraisal can be rapidly and accurately performed at the bedside. The establishment of a service based on the use of the rapid infrared CO_2 analyzer in two general hospitals has increased the recognition of ventilatory failure, and has resulted in more prompt and adequate therapy.

PHYSIOLOGICAL BACKGROUND

The adequacy of ventilation is best measured by the arterial CO_2 tension, (also known as arterial PCO_2 or partial pressure of CO_2 in the arterial blood). Alveolar ventilation is inversely proportional to arterial CO_2 tension. An elevation of the arterial PCO_2 is caused by either primary CO_2 retention due to inadequate alveolar ventilation, or is secondary to a metabolic alkalosis, when the respiratory system tries to compensate by reducing ventilation and retaining CO_2. Although these two conditions can usually be differentiated clinically, the full evaluation of a patient's acid-base status can only be accomplished by knowing two of three parameters: arterial PCO_2, pH, and CO_2 content.

Plasma bicarbonate or an elevated CO_2 combining power is often used to diagnose respiratory acidosis, but it is quite unreliable. Peters and Van Slyke [*1*] pointed this out in 1931. We reviewed the data of twenty-three patients with *chronic* pulmonary failure in whom the diagnosis was confirmed by a markedly elevated PCO_2 (60 mm. Hg or above). Of these twenty-three patients, the serum bicarbonate was definitely elevated in only 30 per cent, borderline in 44 per cent, and completely normal in 26 per cent.

TABLE 1
SERUM BICARBONATE IN CHRONIC RESPIRATORY ACIDOSIS*
(Arterial PCO_2 60 mm. Hg or above)

	Patients	
	No.	%
Normal range (26 to 33 mEq./L.)	6	26
Borderline (34 to 38 mEq./L.)	10	44
Definitely elevated (39 to 44 mEq./L.)	7	30

* Serum bicarbonate determined by a modified Van Slyke titration method.

(Table 1.) In *acute* pulmonary failure the elevation bicarbonate would not be expected as renal retention requires twenty-four hours or more to accomplish this.

As stated, the adequacy of ventilation is best measured by arterial CO_2 tension. Few hospitals, however, are prepared to check arterial PCO_2 except, perhaps, on a research basis. Fortunately carbon dioxide is an extremely diffusable gas, so that arterial and mean alveolar levels of CO_2 are in equilibrium. In normal subjects and in patients without a pulmonary pathologic condition, it is possible to estimate directly the arterial CO_2 tension by the infrared CO_2 analyzer, using a simple catheter from the nose to sample alveolar gas [*2*]. In patients who have ventila-

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tory distribution abnormalities of the lungs, such as occur in emphysema, this direct catheter sample is not valid, and the "rebreathing method" of sampling must be used.

Collier [*3*] has shown that the mixed venous CO_2 tension can be measured by the CO_2 analyzer when the "rebreathing method" is used. Hackney and associates [*4*] have shown that subtracting 6 mm. Hg from the mixed venous PCO_2 value will give an acceptably accurate estimation of the arterial PCO_2, even in patients with severe heart disease or emphysema. The results of over fifty simultaneous tests (Fig. 1) show a good correlation between this method of determining arterial CO_2 tension and the usual method of arterial blood gas analysis. The "rebreathing method" therefore allows a clinically valid estimation of the arterial PCO_2 in all patients, even those with severe CO_2 retention.

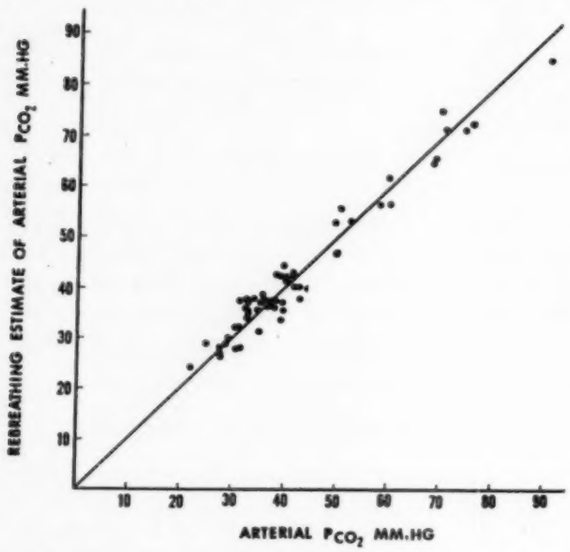


FIG. 1. This correlation graph shows the results of the "rebreathing method" used in over fifty patients to estimate arterial PCO_2 as compared with the simultaneous measurement of arterial PCO_2 by blood gas analysis.

METHODS

Figure 2 shows the CO_2 analyzer* set up for the "rebreathing method." The patient rebreathes from a small rubber bag previously filled with CO_2 of known concentration, usually 8 per cent CO_2 in air, but in patients with respiratory failure higher concentrations of CO_2 must be used. In four to six breaths the concentration in the bag, in the lungs, and in the mixed venous blood comes into equilibrium. The rebreathed gas is constantly being drawn through the analyzer from the system, and the mixed venous CO_2 concentration is directly recorded. The arterial CO_2 tension is calculated as described.

This test can be performed at the bedside by a technician, and the results obtained in five to ten minutes. It can be repeated frequently, and does not require arterial puncture or blood gas analysis. It can be made on confused or comatose patients.

* Liston-Becker (Model 16) CO_2 Analyzer, Beckman Instrument Co., Belmont, California.

RESULTS

We have used this rapid CO_2 analyzer service to determine the ventilatory status of over six hundred patients on the wards of the White Memorial and Los Angeles County Hospitals, and have found ventilatory failure in patients with numerous conditions. (Table II.)

TABLE II
CONDITIONS WHICH HAVE CAUSED VENTILATORY FAILURE IN PATIENTS STUDIED

Paralytic poliomyelitis	Barbituate poisoning
Cerebrovascular accidents	Marked obesity with polycythemia
Infectious neuronitis	Post-thorocotomy deformity
Myesthenia gravis	Pulmonary fibrosis
Progressive muscular atrophy	Thoracic scoliosis
Porphyria	Asthma with excessive sedation
Scleroderma	Emphysema
Insecticide poisoning	

In many of these patients, who were found to be in ventilatory failure, this diagnosis was not considered at first, but when thought of was easily established with the aid of the CO_2 analyzer service. Not until the ventilatory failure was treated did the patients improve. Frequently these patients were being treated for intractable congestive heart failure, while ventilatory failure was really their chief problem.

We studied twenty patients with emphysema who had definite clinical evidence of cor pulmonale. All twenty showed decreased ventilation with CO_2 retention (arterial PCO_2 more than 50 mm. Hg, mean PCO_2 62.5 mm. Hg). We subsequently studied 110 consecutive patients selected only because they had congestive heart failure, to determine if heart failure alone, in the absence of lung disease, was accompanied by CO_2 retention. (Table III.) Some patients in this group had CO_2 retention, but on closer study they were found to have associated pulmonary disease. The rest of the patients had normal or increased ventilation.

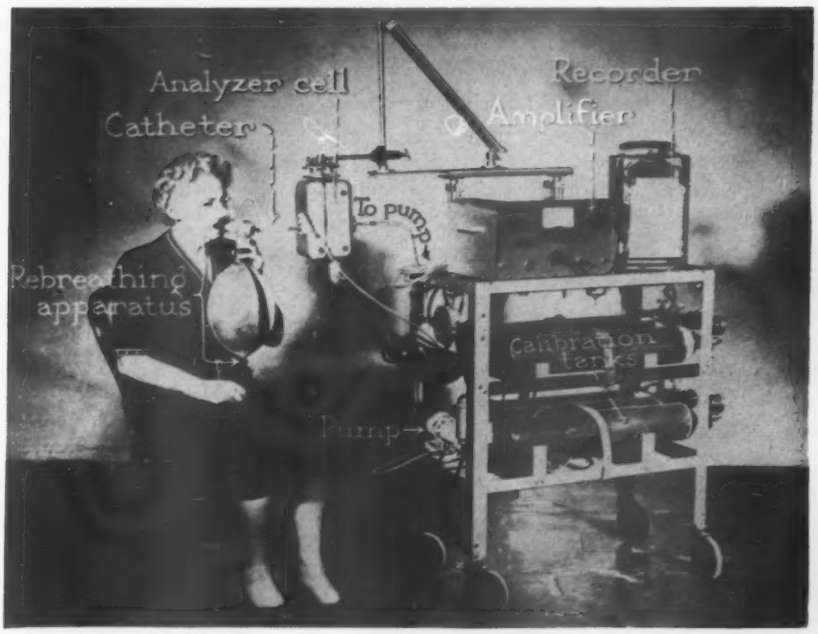


FIG. 2. The CO_2 analyzer as used for the "rebreathing method" of estimating arterial PCO_2.

It is known that when O_2 therapy is used in patients with ventilatory failure it should be given cautiously, since the principal respiratory stimulus in these advanced cases is apparently the lack of O_2. Oxygen therapy may remove this drive to breathing with a further decrease in ventilation, and thus produce or increase CO_2 narcosis in these patients.

The method that we have used to determine whether or not oxygen therapy is safe, is to check the PCO_2 with the analyzer, before and during oxygen administration. If the PCO_2 rises significantly, oxygen therapy should be combined with some method to increase ventilation. This, at times, can be accomplished by intermittent positive pressure breathing, although a tracheotomy or a mechanical respirator may be required.

TABLE III

DETECTION OF VENTILATORY FAILURE IN PATIENTS WITH CONGESTIVE FAILURE

	Ventilatory Status Determined by Estimated Arterial PCO_2 (PCO_2 mm. Hg)					
	Below 30 (hyper-ventilation)	30 to 34 (possible hyper-ventilation)	35 to 45 (normal ventilation)	46 to 50 (possible hypo-ventilation)	51 to 60 (hypo-ventilation)	Above 60 (marked hypo-ventilation)
No. patients in congestive failure with:						
Group A,* no known lung disease	33	27	30	6	..	..
Group B,* definite lung disease	2	1	4	1	3	..
Group C,* emphysema and cor pulmonale	..	..	..	..	9	14

* One hundred ten consecutive patients were selected only on the basis of having congestive failure. Those patients with PCO_2 above 45 mm. Hg were restudied for pulmonary disease. Group C includes three of the 110 patients who were found to have cor pulmonale, plus twenty patients with known emphysema and cor pulmonale.

CASE REPORTS

Some problems of diagnosis and management of respiratory failure are illustrated by the following patients:

CASE I. The patient was a fifty-six year old man who was markedly dyspneic, orthopneic and cyanotic

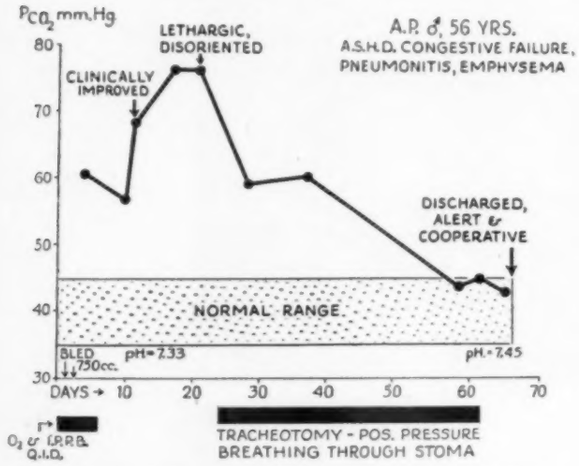


FIG. 3. Estimated arterial PCO_2 as related to the clinical course and treatment of a patient with emphysema, pneumonitis and congestive failure in ventilatory failure.

on admission and whose neck veins were distended. His blood pressure was 140/90 mm. Hg; respiration, 24; temperature, 104°F. The heart was definitely enlarged. There were rales in both bases, with expiratory wheezes. The liver was enlarged two finger-breaths below the costal margin. He had pitting edema of the legs. His electrocardiogram was abnormal, but the changes were non-specific.

A diagnosis of arteriosclerotic heart disease with congestive failure, pneumonitis, and pulmonary emphysema was made.

The patient (Fig. 3) had 22 gm. per cent hemoglobin, and two 750 cc. phebotomies were performed. The infrared CO_2 analyzer showed a high arterial PCO_2 of 60 mm. Hg, (normal 35 to 34 mm. Hg) therefore he was presumed to be in ventilatory failure.

Medical management included the administration of oxygen, antibiotics, digitalis and diuretics. Oxygen with intermittent positive pressure breathing four times a day was used for a few days. The patient clinically improved, but a repeat analysis showed that the PCO_2 had risen, and ventilatory failure was confirmed by the arterial pH of 7.33. Three weeks after admission the patient became lethargic and disoriented. A PCO_2 at this time on two occasions was 76 mm. Hg. Therefore a tracheotomy was performed and automatically cycled positive pressure breathing with O_2 was given continuously through the stoma. The patient promptly improved, the PCO_2 gradually fell to normal and remained normal after the tracheostoma was closed by a plastic tracheotomy plug. The patient was in good condition when discharged. He has had periodic recurrences of lethargy and confusion associated with respiratory failure. These episodes have responded rapidly to similar management, and he has again been well for periods of over a month. Detailed studies on this patient will be presented in a subsequent paper.

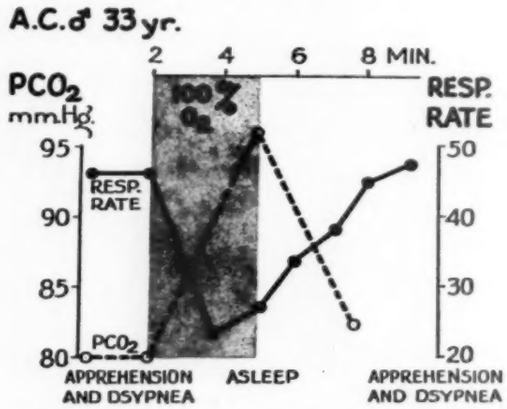


FIG. 4A. Effect of oxygen by nasal catheter upon patient with emphysema—a decreased respiration rate, an increased arterial PCO_2 and CO_2 narcosis was precipitated. These changes were reversed with discontinuance of O_2.

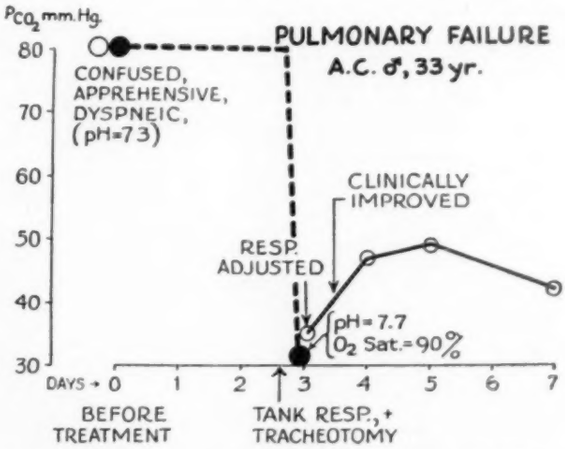


FIG. 4B. Same patient as 4A. Estimated arterial PCO_2 as related to clinical course and treatment. (Normal PCO_2 35 to 45 mm. Hg—shaded line, mean normal; solid circles—arterial PCO_2 as determined by blood gas analysis.)

CASE II. This patient was a thirty-three year old man who had a childhood history of rheumatic fever. When first seen on the ward, he was apprehensive, orthopneic, cyanotic, and edema of the ankles was present.

A diagnosis of rheumatic heart disease with congestive failure was made. Due to the cyanosis and dyspnea, an infrared CO_2 analysis was requested to rule out ventilatory failure. The arterial CO_2 tension

was estimated as 81 mm. Hg. (Fig. 4A.) He was given oxygen by nasal catheter. The respiratory rate markedly decreased, and he fell asleep. The interne commented that the patient had certainly improved, and was resting better with oxygen. However, recheck by the CO_2 analyzer showed that the slower respiratory rate had increased the CO_2 retention, and that the arterial PCO_2 at this time had risen from 81 to 96 mm. Hg. The patient had CO_2 narcosis. Oxygen therapy was stopped, and the respiratory rate gradually increased. As the CO_2 was blown off by the increased respiration the patient awoke and the arterial PCO_2 returned approximately to its former level.

This patient (Fig. 4B) did not improve clinically on routine treatment, therefore a tracheotomy was performed and a tank respirator used. It was anticipated that ventilating him would be difficult, therefore the respirator was set for maximum pressures. A recheck of the PCO_2 and the arterial pH determinations showed that he was now being hyperventilated and had respiratory alkalosis. After proper ventilation was established by decreasing the respirator pressures, he began to improve rapidly.

In both of these patients ventilatory failure was first established by the CO_2 analyzer service. It was not until the ventilatory failure was definitely diagnosed and proper treatment instituted that the patients really improved.

COMMENTS

In emphysema, as the disease advances, hypoventilation with ventilatory failure becomes the dominant problem. These patients have little respiratory reserve, and infection frequently precipitates acute pulmonary decompensation. Hypoventilation results in a high arterial carbon dioxide tension and acidosis, and a low oxygen saturation [*5*].

Increase of ventilation is the primary objective of treatment in these patients. Hypoxemia is present in all patients with ventilatory failure when breathing room air. While oxygen therapy will relieve the hypoxemia, only increased alveolar ventilation will relieve the CO_2 retention and respiratory acidosis. As previously established [*5,6*], O_2 therapy may in some instances result in further CO_2 retention and lead to CO_2 narcosis. This may be suspected clinically when lethargy or a marked decrease in respiratory rate occurs with O_2 therapy, as in our second case. If adequate alveolar ventilation can be achieved by mechanical means or by relief of airway obstruction, not only will the respiratory acidosis be relieved, but the alveolar O_2 tension will be elevated even while breathing room air. This elevation of the alveolar O_2 tension will usually result in relief of a major portion of the hypoxemia, the amount being dependent on the degree of abnormal pulmonary blood and gas distribution.

Successful treatment of patients with ventilatory failure from chronic lung disease, by the use of mechanical artificial respiration, has been reported by several authors [*7–10*], and is illustrated by our cases.

It should be re-emphasized that ventilatory failure occurs in many conditions and that in contradistinction to congestive heart failure, in which the clinical symptoms are usually sufficient to make the diagnosis, the symptoms of ventilatory failure are usually ill defined and a laboratory test is necessary to establish the diagnosis. It is fortunate that the arterial PCO_2 is related to ventilation, and therefore can be used to determine the ventilatory status. We believe that the estimated PCO_2 by the "rebreathing method" as described is a rapid, practical test for ventilatory failure.

Since the rapid infrared CO_2 analyzer service has been available in our hospitals, the utility of this laboratory test has seemed to be comparable to blood sugar determination in diabetes or the non-protein nitrogen determination in uremia. There has been an increased frequency of the diagnosis of ventilatory failure in our hospitals since the staff has been alerted to the fact that this is a common condition which appears in many diseases. Prior to the establishment of this service this was a rare diagnosis, except in patients with poliomyelitis. Since this service has been established, non-polio ventilatory failure has been diagnosed in over fifty cases in the past two years. Over half of these during the last nine months, and recently in a one-week-period five such patients were found and immediately treated, with good results.

SUMMARY

1. Ventilatory failure is difficult to diagnose from signs and symptoms alone.

2. The rapid infrared CO_2 analyzer using the "rebreathing method" offers a simple, reliable test for ventilatory failure which can be performed on the ward by a technician in less than ten minutes. It can be performed on all types of patients, even on those who are comatose or confused.

3. CO_2 narcosis can be easily diagnosed with the aid of the analyzer with the "rebreathing

method," and mechanical measures to increase ventilation can be instituted. The safety of oxygen therapy in these patients can be readily determined.

4. The establishment of an infrared CO_2 analyzer service on the wards of two general hospitals has alerted the staff to the frequency of ventilatory failure in many conditions other than poliomyelitis. Increasing numbers of these patients are now being recognized and treated.

Acknowledgment: The authors wish to express their appreciation to Mrs. Grace Daniells, Mrs. Virginia McDonald and Mrs. Trellis Starks for technical assistance.

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Studies on the Regulation of the Coronary Circulation in Man*

I. Atropine-induced Changes in Cardiac Rate

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INCREASE in cardiac rate results in a decrease in time available for filling of the coronary arteries. In an isolated system, a shortened inflow time would lead to a decreased coronary inflow per minute, as indeed was shown by Anrep [*1*].

On the other hand, changes in coronary flow are linked to changes in oxygen metabolism [*2*]. Isolated heart [*3*] and heart-lung studies [*4*] showed that myocardial efficiency decreased as heart rate increased, indicating either an increase in oxygen utilization or a fall in cardiac work. Recent experiments on the intact anesthetized dog have demonstrated that for a given level of cardiac work, myocardial oxygen consumption and coronary flow rose as cardiac rate increased [*5–7*].

It is the purpose of this report to describe the effects of atropine cardioacceleration in man and to demonstrate the effects of such changes in rate within the physiological range on coronary blood flow, myocardial oxygen utilization, cardiac work, and filling pressure.

MATERIAL AND METHODS

Six patients were studied by cardiac catheterization: three had functional systolic murmurs; one had diastolic murmur of aortic insufficiency (patient L. T.) without major change in blood pressure; one had mitral stenosis (patient G. T.) with a valve area of 1.0 sq. cm.; and the third patient had a mild mitral insufficiency (B. H.) with a valvular regurgitation equal to 25 per cent of the forward flow as determined by the Korner-Shillingford method [*8*].

Cardiac catheterization was performed in the usual fashion and an indwelling thinwall No. 18 Riley needle placed in the brachial artery. If diagnostic studies were required, as in the first three patients, these were carried out before the start of the investigation. Pressures were recorded in the pulmonary capillary wedge position, pulmonary artery, right ventricle, and right atrium. Cardiac output was measured by the indicator dilution technic [*9*] using T-1824 Evans blue dye in three patients, and by the direct Fick method in all six. Within five minutes of determination of the Fick output, the catheter was inserted into the coronary sinus. Coronary blood flow, calculated as cc./100 gm. of left ventricular muscle/minute, was then measured by the nitrous oxide desaturation breathing technic of Kety and Schmidt [*10*] as modified by Goodale and Hackel [*11*]. During the eight minutes required for determination of coronary flow, arterial blood pressure, heart rate and the indicator dilution outputs were also measured. Following completion of control observations, 1 to 1.4 mg. of atropine sulfate were administered slowly intravenously. When the full effect had been obtained and the rate stabilized (approximately ten to fifteen minutes), a repeat coronary blood flow (and arterial-pressure, heart rate and dilution output) was measured. The catheter then was advanced again to the pulmonary wedge position with successive measurement of pressures, and a Fick cardiac output as described in the control observations.

Blood samples drawn from the coronary sinus, pulmonary artery and brachial artery, were analyzed for oxygen and CO_2 content by the technic of Van Slyke and Neil [*12*]. Multiple blood samples were collected fractionally every two seconds from the brachial artery immediately following the injection of T-1824. Following centrifugation, the concentration of blue dye in the plasma was analyzed spectrophotometrically and calculation of the cardiac output, both forward and regurgitant, performed according

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TABLE I
EFFECT OF ATROPINE ON THE GENERAL CIRCULATION

Patient	Age (yr.)	Diagnosis	Body Surface (area M^2)	Cardiac Output (L./min./M^2)	Pressures (mm. Hg)						Ventricular Work (kg. M/min./M^2)	
					Brachial Artery			Pulmonary Arterial Mean	Right Atrial Mean	Pulmonary Capillary Mean	Left	Right
					Systolic Mean	Mean	Diastolic Mean					
E. S.	29	N	1.5	4.4	92	80	73	13	5	9	5.0	0.7
		*	....	4.2	94	82	76	11	3	7	5.1	0.7
O. M.	24	ASm	2.08	3.9	110	90	85	19	4	12	5.2	0.8
		*	....	3.6	115	105	93	17	3	13	5.1	0.64
L. T.	21	AIm	1.75	4.7	105	86	77	12	0	10	6.2	0.77
		*	....	4.0	98	89	78	10	0	6	5.2	0.57
G. T.	42	MS	1.95	3.0	120	95	85	34	9	20	4.7	1.0
		*	....	2.6	118	95	85	..	7	....	4.0	....
B. H.	21	MI	1.57	4.2	115	85	77	15	5	9	6.1	0.29
		*	....	4.6	110	90	82	16	3	7	6.2	0.51
B. K.	31	N	1.72	3.1	108	88	79	14	4	8	4.2	0.46
		*	....	3.4	107	87	82	13	2	5	4.9	0.40
Average	..	...	....	3.9	108	87	79	15	5	10	5.2	0.60
		*		3.7	107	91	83	13	3	7.5	5.1	0.56

NOTE: N = normal, before atropine.
ASm = aortic systolic murmur only.
AIm = aortic diastolic murmur only.
MS = mitral stenosis.
MI = mitral insufficiency.
* After atropine.

to previously described technics [*8,9*]. Systolic and diastolic mean pressures and systolic and diastolic time periods were measured on the brachial arterial pressure pulse recorded during the coronary flow.

Coronary vascular resistance was calculated by the standard formula:

$$CVR = \frac{BAm - RAm \times 1332}{CF}$$

where CVR = coronary vascular resistance (dynes second cm^{-5}); BAm = brachial arterial mean pressure, mm. Hg.; RAm = right atrial mean pressure, mm. Hg.; CF = coronary flow cc./100 gm./second; 1332 = conversion of mm. Hg to dynes/cm^2.

Gregg has shown that about 75 per cent of coronary flow takes place in diastole [*13*]. A more exact estimate of coronary arteriolar resistance during the phase of highest flow, is obtained from a formula which considers: (1) the fraction of coronary flow occurring during diastole and (2) the true rate of flow of blood through the coronary vessels, i.e., during the seconds of diastole; and (3) the pressure gradient during diastole. Hence, the following formula was devised:

$$CVRd = \frac{(BAdm - RAm) \times DFP \times 1332}{CF \times 0.75}$$

where CVRd = diastolic coronary vascular resistance (dynes second $cm.^{-5}$)
DFP = diastolic filling period, second/minute
0.75 = fraction of coronary flow occurring in diastole [*13*]

Observations. General hemodynamic changes: (Table I.) Cardiac output, mean arterial blood pressure and systolic mean blood pressure were essentially unchanged in five of six patients. There was an insignificant rise in the diastolic mean pressure of 4 mm. of mercury. Pulmonary arterial pressure was unaltered while pulmonary wedge and right atrial pressures showed a consistent 2 mm. decrease Left and right ventricular work per minute showed little change.

Cardiac rate and its effect on cycle periods: (Table II.) The average cardiac rate was 70 before and 97 after administration of atropine or a 38 per cent increase

TABLE II
EFFECT OF ATROPINE ON THE CORONARY CIRCULATION

Patient	Heart Rate (per minute)	Systolic Time (sec./min.)	Diastolic Time (sec./min.)	Coronary Flow (cc./100 gm./min.)	Coronary Sinus			A-V (O_2 cc./L.)	Myocardial O_2 Consumption		Coronary Vascular Resistance (dyne second cm.$^{-5}$)	
					O_2 Content (vol. %)	O_2 Saturation (%)	pO_2 (mm. Hg)		O_2 (cc./100 gm./min.)	O_2 (cc./100 gm./systolic sec.)	Mean	Diastolic
E. S.	63*	21.5	38.5	70	5.7	37	24	9.9	7.0	0.32	85.7‡	66.6‡
	96†	29.0	31.0	120	6.9	44	27	8.5	10.0	0.34	52.6	33.5
O. M.	62*	22.0	38.0	57	5.8	30	21	13.1	7.5	0.34	121.0	95.7
	87†	29.5	30.5	79	5.6	30	19	13.3	10.5	0.36	103.5	61.7
L. T.	82*	25.4	34.6	83	6.5	36	23	12.3	10.2	0.40	83.0	57.0
	100†	30.0	30.0	104	6.6	36	22	11.6	12.0	0.39	68.6	40.0
G. T.	62*	22.0	38.0	80	6.0	32	..	13.2	10.6	0.48	86.0	64.2
	90†	29.0	31.0	91	5.4	29	..	13.5	12.3	0.42	77.4	47.2
B. H.	80*	25.6	34.4	96	4.8	28	18	11.9	11.5	0.44	66.7	45.8
	108†	29.7	30.3	126	4.8	28	18	11.9	15.0	0.50	55.2	33.7
B. K.	70*	24.0	36.0	58	6.1	33	22	12.1	7.0	0.30	116.0	81.7
	102†	30.0	30.0	94	5.8	33	21	11.9	10.3	0.37	72.3	45.3
Average	70*	23.4	36.6	74	5.8	33	22	12.1	8.9	0.380	93.0	68.6
	97†	29.5	30.5	102	5.8	33	21	11.8	11.9	0.396	71.6	43.6

* Before atropine.
† After atropine.
‡ $\cdot \times 10^3$.

over the control. With this increase in cardiac rate, there was an increase in the total duration of systole per minute of 6.1 seconds or 26 per cent with a corresponding decrease in the total time available for diastole per minute.

Myocardial oxygen consumption and coronary flow: (Table II.) Myocardial oxygen consumption in cc./100 gm./minute increased from 8.9 to 11.9 or a 33 per cent increase.* If oxygen consumption per 100 gm. is now computed as a function of the number of seconds of systolic contraction per minute, $\frac{\text{cc. } O_2/100 \text{ gm./minute}}{\text{systolic sec./minute}}$ it can be shown that the average resting oxygen consumption per systolic second was 0.379 cc. Following atropine cardioacceleration, oxygen consumption per systolic second was virtually unchanged at a value of 0.396 cc. The increase in oxygen consumption per minute paralleled directly the six second increase in cardiac contraction time per minute.

* The difference between the mean values is three times the standard error. While statistical methods are not strictly applicable to such a small sample, these data would at least suggest an unlikelihood that the differences were due to chance.

Coronary arteriovenous oxygen extraction was essentially unchanged by atropine. Average resting coronary blood flow was 74 cc./100 gm./minute, a figure 20 per cent lower than reported in four patients studied by the desaturation technic by Goodale and Hackel [*11*]. Flow increased to 102 cc./100 gm./minute, a 38 per cent increase over the control value. The change was proportional to the increase in myocardial oxygen consumption.

Relation of myocardial oxygen consumption to cardiac work: (Fig. 1.) Oxygen consumption as measured by the coronary sinus technic represents that of left ventricular muscle [*13*]. There was little major change in average left ventricular work per minute with cardioacceleration (Table I), yet oxygen consumption was increased. The less striking changes in coronary flow and myocardial oxygen consumption in the patients L. T. and G. T. are believed related to the fact that cardiac work actually decreased at the same time that the heart rate increased.

Coronary vascular resistance and coronary flow: (Table II.) Mean coronary vascular resistance decreased by 22 per cent. When however, resistance during diastole was calculated, assuming that three-quarters of coronary flow took place during diastole

[*13*], the reduction in resistance was 36 per cent. This latter figure, derived from a formula which encompasses both the increase in coronary flow and also the decrease in time available for diastolic inflow, probably represents a truer approximation of the magnitude of change in the cross sectional area of the coronary arteriolar bed.

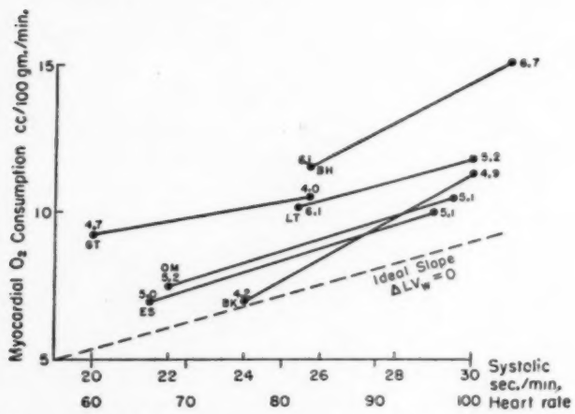


FIG. 1. Effect of atropine cardioacceleration on myocardial oxygen consumption. Myocardial oxygen consumption is plotted on the ordinate. Both cardiac rate and the resulting increase in systolic contraction time are plotted on the abscissa. The "ideal slope" is a hypothetical line signifying the increase in oxygen consumption due to rate alone, assuming no change in cardiac work ($\Delta LV_w = 0$). The amount of increase is directly related to the increase in number of systolic seconds per minute.

Miscellaneous Observations. Isolated studies at varying heart rates tend to confirm the findings following administration of atropine. (Table III.) Note that patient R. S. performed normal cardiac work, but at a low total oxygen cost because his rate was only 55. Similarly, patient A. Z. had an even lower oxygen consumption and coronary flow because both heart work and rate were low. On the other hand, in patient R. Sa. with normal ventricular work, oxygen consumption was increased in the presence of a high heart rate.

COMMENTS

Physiological Implications. These findings in man corroborate studies in animals showing that an increased cardiac rate per se, leads to an increased myocardial oxygen consumption. The increase in oxygen consumption (at least within the physiological range) appeared to parallel directly the amount of time spent in contraction per minute. Similarly, Case et al. [*6*] have related myocardial oxygen consumption not only to height, but also to duration of the systolic blood pressure in the experimental animal. At average resting left ventricular work levels, approximately 0.38 cc. of oxygen per 100 gm. were being utilized per second of systole with a minute consumption of 8.9 cc./100 gm. Following a six-second increase in systolic contraction time, oxygen consumption increased to 11.9 cc. per minute (or about 0.4 cc. of oxygen per systolic second). This is not in accord with

TABLE III
RANDOM OBSERVATIONS OF EFFECT OF HEART RATE ON MYOCARDIAL OXYGEN CONSUMPTION

Patient	Diagnosis	Heart Rate	Left Ventricular Work (kg. M/min./M²)	Myocardial Oxygen Consumption	
				(cc./100 gm./min.)	(cc./100 gm./systolic sec.)
R. S.	N	55	4.5	7.1	0.37
A. Z.	MS	59	2.5	5.4	0.28
R. Sa.	MI	130	4.6	13.9	0.56
M. B.	COR disease	105	3.6	8.8	0.29

NOTE: N = normal.
MS = mitral stenosis.
MI = mitral insufficiency.
COR disease = coronary disease.

Starling and Visscher [*4*] who found a decreased oxygen consumption per beat at higher rates. Other factors, however, may have varied.

Myocardial oxygen consumption and coronary flow usually change equally in the same direction [*2*]. Unpublished studies in our laboratory have shown that oxygen is extracted by the myocardium down to a coronary venous pO_2 of 20 mm. Hg [*14*] in normals and grade 1 and 2 cardiacs [*15*]. Unless pH changes, further increases in oxygen consumption are usually met by increases in coronary flow rather than extraction.

Coronary vascular resistance in diastole decreased in the presence of tachycardia, due first, to the increased oxygen demand with increased systolic contraction time, and second, to the decrease in diastolic inflow time. Other compensatory factors played a minor role in increasing flow.

Atropinization produced virtually no other changes in hemodynamics once a steady state had been reached. The rather consistent but small decrease in filling pressure of the two

ventricles (pulmonary wedge and right atrial mean pressures) is similar to the observations of McMichael and Scharpey-Schafer [*16*] and may represent decreased diastolic filling of the ventricles.

Clinical Implications. Increased cardiac rate in the normal individual and the mild cardiac imposes a dual load on cardiac function. It has always been taught that increased cardiac rate decreased the time for diastolic coronary inflow [*17*]. It is now evident that not only is the time for inflow decreased, but that the need for oxygen by the myocardium is increased by the longer period of time spent in contraction [*6*]. We have shown this up to a heart rate of 108. Random observations in man (Table III) and animal studies indicate that higher heart rates further increase oxygen consumption, as well as decrease diastolic inflow time. It must be borne in mind however, that the increase is always relative to a given work load. If output or pressure falls as tachycardia increases, then the total demands for oxygen will decrease [*14*].

Tachycardia, even at rates as low as 150 can produce angina pectoris, coronary insufficiency, acute cardiac failure and shock. Not infrequently, even in apparently normal people, electrocardiographic changes of myocardial ischemia will develop during tachycardia. Cardiac output eventually becomes reduced [*18*] even at rates (less than 180) which do not decrease the "rapid phase" of ventricular diastolic filling [*19*]. The fact that tachycardia not only shortened diastolic filling time for the cardiac chambers and the coronary vascular tree, but also increased myocardial oxygen needs, may well explain the ultimate development of these circulatory derangements.

In the presence of coronary artery disease, usually the coronary bed is near maximal vasodilatation [*20*]. Even within the physiological range of increased heart rate, a 36 per cent reduction in vascular resistance was required to meet the myocardial demand for oxygen. In the presence of severe coronary disease, such a decrease may not be possible. With an increased demand for oxygen beyond that which may be supplied, two patterns develop. If the ischemia is localized, anginal pain results. If ischemia is more generalized, then the requisite cardiac work cannot be done at the high heart rate and failure with or without shock ensues. A similar situation may be seen in severe aortic stenosis and insufficiency.

It is interesting to note the random observations reported earlier in two comparable patients with mitral stenosis. One had a cardiac rate of 130 per minute. Here the oxygen consumption was 13.9 cc./100 gm./minute, thus requiring a high coronary flow. The second patient, with a cardiac rate of only 59, required an oxygen consumption of only 5.4 cc./100 gm./minute and a correspondingly much lower coronary flow. It is evident that the first patient would have easily gotten into difficulty if there were concomitant coronary vascular disease.

The implications of these findings regarding treatment are obvious. Every effort should be made to control cardiac rate in any cardiac emergency. Much has been made of tachycardia in the pulmonary edema or shock of mitral stenosis [*21*]. The same emphasis should be given to tachycardia in the patient with a myocardial infarction or coronary insufficiency.

Tachycardia may result as much from pain and severe anxiety, as from the underlying cardiac lesion. Liberal use of sedation and opiates is advocated—the latter particularly so because of their strong cholinergic effects on heart rate. Similarly, digitalization for shock or congestive failure is helpful, not only by improving myocardial efficiency and contractility, but also by the cumulative effects of a decreased cardiac rate. Knowing that tachycardia places a demand load on the coronary circulation, then it may be reasoned conversely that when the patient is experiencing no symptoms or signs of coronary or cardiac insufficiency, and the electrocardiogram shows no sign of ischemia, that oxygen demands are momentarily being met and the vascular bed has dilated adequately. While no tachycardia should go long untreated, the need for emergent therapy should be governed by the above-mentioned factors.

SUMMARY

The effects of atropine cardioacceleration on coronary flow, cardiac work rate and cardiac oxygen metabolism, have been studied in six patients. A 38 per cent increase in rate resulted in a 38 per cent increase in coronary flow, and 33 per cent increase in oxygen consumption. The increased oxygen consumption was directly related to the increased number of seconds of systolic contraction time occurring with tachycardia. The increased flow was mediated by a decrease in vascular resistance which compensated both for the increased flow and the de-

creased diastolic time. Other hemodynamic consequences of atropinization were inconsequential. The clinical implications of these findings are discussed.

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Analysis of Factors Affecting the Recurrence of Thromboembolism off and on Anticoagulant Therapy*

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NUMEROUS reports [*1–4*] in recent years have indicated a decreased rate of recurrence of embolism and thrombosis when groups of patients with these complications were treated with anticoagulants on a long-term basis. However, although the over-all incidence seems to be markedly reduced, thromboembolism continues to occur in some patients receiving anticoagulants. Furthermore, McDevitt et al. [*4*] recently reported that anticoagulants may be less consistently effective in patients with a very strong tendency to recurrent thromboembolic phenomena.

A more detailed analysis of the records of patients with recurrent thromboembolism has been carried out in order to (1) gain knowledge of the relative benefit derived from long-term anticoagulants by individual patients; (2) assess the clinical factors which might be associated with the failure of anticoagulants to prevent recurrent thrombotic or embolic phenomena; (3) arrive at the most effective and justifiable therapeutic approach to patients with isolated thromboembolic episodes by analyzing factors associated with occurrence of thromboembolic complications in patients off therapy, and (4) check whether or not there is a greater danger of recurrence following discontinuation of anticoagulant therapy (rebound phenomenon).

MATERIALS AND METHODS

This analysis includes case histories of ninety patients followed up in the Long Term Anticoagulant Clinic, the medical wards and the private services of members of the Vascular Research Group of the New York Hospital. The over-all incidence of thromboembolism in these patients, with emphasis on cerebral episodes, was reported previously [*4*]. The two characteristics which applied to all patients were (1) they must have received anticoagulants at some time during their follow-up; (2) they must have had at least one cerebral thromboembolic episode. Periods of observation varied from twenty-four hours to over ten years. Seventy-nine patients were followed up for over six months, seventy-two over one year, sixty-two over two years, forty-three over four years and twenty-nine over six years. A group of forty of the ninety patients, who were followed up for at least six months on and six months off therapy, were analyzed in greater detail. The total length of observation of patients off anticoagulants included periods from the first thromboembolization until anticoagulant therapy was begun, intervals of interruption during the years before it was realized that continuous therapy was more beneficial, and intervals of interruption because of the patients' wishes or need for surgery or travel. This is a group with a generally strong tendency to recurrent thromboembolism; each patient had been referred to members of our staff because of preexisting embolism or thrombosis.

Some of the clinical characteristics of the group are shown in Table I. The miscellaneous sub-group consists mostly of patients with idiopathic recurrent thromboembolism.

Because the clinical differentiation of thrombosis and embolism is often difficult or may be impossible, all the episodes were considered together under the term of thromboembolism.

The technical aspects of follow-up of patients in the Long Term Anticoagulant Clinic of the New York Hospital have been described previously [*4*]. The statistical methods are indicated with the results.

RESULTS

The records of all patients who were followed up for at least six months off and six months on

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TABLE I
CLINICAL DATA

Group	Sub-group	Age* Mean ± S.D.	No. of Patients					
			Total	Women	Arrhythmia	Congestive Heart Failure	Myocardial Infarction	Blood Pressure 150/100 mm. Hg or Over
40 patients followed for at least 6 mo. off and 6 mo. on anticoagulant treatment	Rheumatic heart disease†	43 ± 9	27	20	24	15	4	3
	Arteriosclerotic and/or hypertensive heart disease	57 ± 13	9	4	2	3	7	2
	Miscellaneous	39 ± 20	4	1	1	1	0	0
Total			40	25	27	19	11	5
Total group of 90 patients	Rheumatic heart disease†	44 ± 10	51	34	44	24	5	3
	Arteriosclerotic and/or hypertensive heart disease	61 ± 11	28	12	7	9	15	13
	Miscellaneous	42 ± 17	11	3	3	2	0	4
Total			90	49	54	35	20	20

* At time of first cerebral thromboembolism.
† All patients had mitral stenosis.

therapy were analyzed in order to assess statistically the beneficial effect of anticoagulant treatment. The mean rates and the standard errors of the recurrence of thromboembolism in episodes per month, as well as the 5 per cent and 1 per cent confidence limits of the means, are shown in Table II. The rates during the anticoagulant treatment were much lower in all categories. There was little or no overlap of the mean rates in patients off and on therapy even at the 1 per cent level except for the small sub-group of nine patients with arteriosclerotic heart disease. The four patients with miscellaneous diagnoses were not considered separately. Furthermore, the t-test revealed that the differences between the rates in patients off and on anticoagulant therapy were significant ($p < 0.01$) for the whole group and for the sub-group with rheumatic heart disease, and of borderline significance ($p < 0.05$) for the small sub-group with arteriosclerotic heart disease.

In order to appraise the benefit derived from anticoagulant therapy by individuals rather than by the group as a whole, all ninety patients were grouped according to the number of recurrences off and on anticoagulant therapy following the first thromboembolic episode. Table III indicates that in sixty-one patients there were more episodes when the patients were not receiving anticoagulants. In nineteen patients the number of recurrences was equal in the patients off and on therapy, whereas in ten patients more episodes occurred while they were receiving anticoagulants.

However, this table does not take into account the length of time over which various patients were followed up while they were off and on treatment. Therefore, a fourfold contingency table comparing the days with and without thromboembolic episodes in patients off and on anticoagulant therapy was constructed as illustrated in Table IV for each of the forty patients included in the previous statistical analysis. A difference between the product of a times d, minus the product of b times c was calculated for each patient (e.g., $3 \times 1784 - 0 \times 1267 = +5352$ for patient E. M. in Table IV). Positive and negative values were considered to reflect, respectively, benefit and lack of benefit obtained from anticoagulant treatment.

A positive value was obtained in thirty-three of the forty patients by this method. Application

TABLE II

THE RATE OF RECURRENCE OF THROMBOEMBOLISM IN EPISODES PER MONTH

Group and Therapy	Mean	Standard Error of the Mean	Confidence Limits		P
			5%	1%	
The entire group (40 patients):					
Rate off anticoagulants	0.127	0.0248	0.077–0.177	0.060–0.194	.....
Rate on anticoagulants	0.029	0.0068	0.015–0.043	0.011–0.047	.....
Rate off anticoagulants minus rate on anticoagulants	0.098	0.0248	0.048–0.148	0.031–0.165	<0.01
Rheumatic patients (27 patients):					
Rate off anticoagulants	0.117	0.0231	0.069–0.165	0.053–0.181	.....
Rate on anticoagulants	0.032	0.0085	0.014–0.050	0.008–0.056	.....
Rate off anticoagulants minus rate on anticoagulants	0.085	0.0220	0.040–0.130	0.024–0.146	<0.01
Arteriosclerotic and/or hypertensive patients (9 patients):					
Rate off anticoagulants	0.082	0.0139	0.050–0.114	0.035–0.129	.....
Rate on anticoagulants	0.023	0.0149	0 –0.057	0 –0.073	.....
Rate off anticoagulants minus rate on anticoagulants	0.059	0.0233	0.005–0.113	(−0.019)–0.137	<0.05

of the sign test to this result gave a P value of less than 0.001, indicating again that sampling variation was extremely unlikely to account for the lower incidence of thromboembolism in patients on therapy.

TABLE III

RECURRENCE OF THROMBOEMBOLIC EPISODES IN PATIENTS ON AND OFF THERAPY (NUMBER OF PATIENTS)

		No. of Episodes on Anticoagulants					
		0	1	2	3	4–6	Over 6
No. of episodes off anticoagulants (excluding the first episode)	0	11	3	1	..	..	..
	1	19	6	..	2	..	..
	2	13	3	1	..	1	..
	3	8	1	1	1	1	..
	4–6	3	4	3	1	..	2
	over 6	3	..	1	..	1	..

A more rigid test was applied by calculating the chi-square value for each patient from the same fourfold contingency table. In eleven of the forty patients a P value of less than 0.05 obtained from the chi-square indicated that the treatment was of significant benefit. In the remaining patients the value did not reach a statistically significant level, although in the majority of them benefit from the treatment was apparent when the less critical sign test was applied, as already indicated.

TABLE IV

PATIENT E. M. (EXAMPLE)

Anticoagulant Therapy	Days with Thromboembolic Episodes	Days without Thromboembolic Episodes
Off	3 (*a*)	1267 (*b*)
On	0 (*c*)	1784 (*d*)

The P values were then plotted against certain variables in order to assess factors which might be responsible for the presence or the apparent absence of a significant benefit. It was found that the higher the rate of recurrence while the patients were not receiving anticoagulants, the higher, on the whole, was the P value. The length of anticoagulant therapy was another factor important in bringing out a significant effect of anticoagulant treatment in most cases. With one exception, no P values of less than 0.05 were obtained in patients who received anticoagulants for less than two years. On the other hand, no suggestive trend was apparent when the P values

TABLE V

THE INCIDENCE OF CARDIOVASCULAR COMPLICATIONS IN PATIENTS WITH AND WITHOUT THROMBOEMBOLISM ON ANTICOAGULANT THERAPY

Group	No. of Patients		No. and Percentage of Patients with Complications				
			Whole Group			Rheumatic	
	Total	Rheumatic	Myocardial Infarction	Arrhythmia	Congestive Heart Failure	Mitral Regurgitation	Lesion of Other Valves
Patients with thromboembolic episodes on anticoagulant therapy...	17	12	7 (41%)	12 (71%)	12 (71%)	10 (83%)	6 (50%)
Patients without thromboembolic episodes on anticoagulant therapy	23	15	4 (17%)	14 (61%)	7 (30%)	10 (67%)	3 (20%)
P.....	..	..	<0.2	<0.9	<0.05	<0.3	<0.3

were plotted against the rate of recurrence in patients on therapy or against the length of time during which the patients were observed off therapy. A combination of the two factors, which appeared to correlate with the P values by obtaining the product of the length of anticoagulant

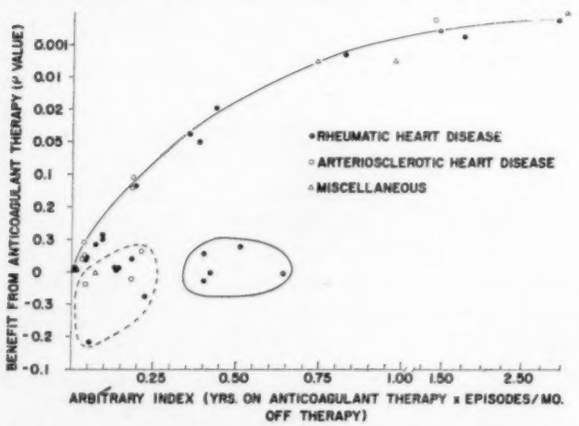


FIG. 1. The relationship of the length of anticoagulant therapy and of the recurrence rate of thromboembolism in patients off therapy to the "relative benefit" from treatment.

treatment in years times the rate of recurrence in patients off anticoagulants, gave an arbitrary index against which the P values were plotted as illustrated in Figure 1.

The patients who failed to show a benefit in spite of an adequate length of treatment and a high rate of thromboembolism off therapy could be identified as those represented by the points far off the general curve of the graph. These five patients (points encircled by the continuous line on the figure) all had severe rheumatic heart disease with mitral stenosis, atrial fibrillation and congestive heart failure. In four, mitral insufficiency was present in addition to the stenosis, two patients had an associated aortic stenosis and two had suffered a myocardial infarction in addition. Thus it is clear that these patients were all in advanced stages of their disease. Four of the five patients were in the fifth decade of life, the fifth was in the third decade.

The patients represented by the points encircled by the interrupted line in Figure 1 showed a slight tendency to fall off the general curve of the graph, although their index was still comparatively low. This group included, with two exceptions, all the patients who had had one or more thromboembolic episodes during anticoagulant therapy.

The prevalence of non-thromboembolic cardiovascular complications in patients with and without thromboembolism on anticoagulant therapy is shown in Table v. All the complications which were analyzed were found to be common amongst those who experienced thromboembolism on treatment. The presence of congestive heart failure, in our series, appears to be the most important, the difference in its incidence being statistically significant (chi-square = 4.812, $P < 0.05$), indicating that on the whole cardiac function was more severely impaired in the patients who experienced thromboembolic episodes while under anticoagulant treatment than in patients without

TABLE VI

THROMBOEMBOLISM IN PATIENTS WITH AND WITHOUT CONGESTIVE HEART FAILURE

Group	No. of Patients	Rate of Recurrence in Episodes Per Month		No. of Thromboembolic Episodes			
				Off Anticoagulant Therapy		On Anticoagulant Therapy	
		Off Therapy	On Therapy	Pulmonary	Systemic	Pulmonary	Systemic
Congestive heart failure	19	0.127	0.050	16	87	14	27
No congestive heart failure	21	0.127	0.009	7	71	4	2
Total	40	0.127	0.029	23	158	18	29

thromboembolism on treatment. This was confirmed, as illustrated in Table VI, by the smaller reduction of the recurrence rate during anticoagulant therapy in patients with congestive heart failure than in those without failure. The recurrence rate during anticoagulant treatment was significantly higher in patients with failure than in patients without this complication ($t = 2.412$, $P < 0.05$). However, there was no difference during the periods the patients were off treatment. Also, when the patients with rheumatic heart disease were considered separately there was no significant difference between the recurrence rates of patients with and patients without failure during the periods they were off therapy, but there was a significant difference during anticoagulant therapy ($t = 3.071$, $P < 0.01$). A similar trend was apparent in patients with arteriosclerotic heart disease, although the difference between the rates of recurrence in patients with and without failure during anticoagulant treatment did not reach a statistically significant level in this small group ($t = 1.727$, $P < 0.2$).

Table VI also shows the relative incidence of pulmonary and systemic thromboembolism. Although the number of both pulmonary and systemic episodes was lower during anticoagulant therapy, the pulmonary episodes accounted for twenty-three (13 per cent) of all thromboembolic episodes occurring in patients off treatment and for eighteen (38 per cent) of those occurring in patients during treatment. This difference is highly significant (chi-square = 14.876, $P < 0.001$). There was no significant difference in the relative incidence of pulmonary and systemic thromboembolism between the groups with and without congestive failure. The same was found when patients with rheumatic and arteriosclerotic heart disease were considered separately.

The rate of recurrence of thromboembolic episodes during various periods following a previous episode was calculated in order to determine whether or not the danger of recurrent thromboembolism was greater shortly after a previous episode. This analysis is based on the records of all ninety patients. Figure 2 shows that the rate during the periods the patients were off anticoagulant treatment, symbolized by the filled blocks, was highest during the first week after a previous episode and declined with time although it reached a comparative plateau after the first six weeks. The differences between the

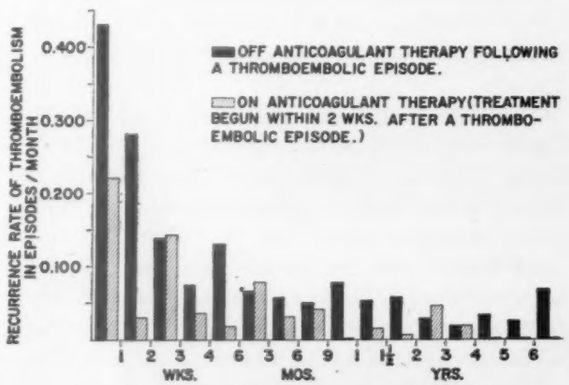


FIG. 2. Time-course of the recurrence rate of thromboembolism in patients off and on anticoagulant therapy in relation to a previous thromboembolic episode. Based on the records of ninety patients.

recurrence rates during the first three weeks and the second three weeks, and between the second three weeks and the period from six weeks to six years were statistically significant at the 1 per cent level (chi-square test). No striking decline in the recurrence rate could be demonstrated following the first six weeks after a thromboembolic episode.

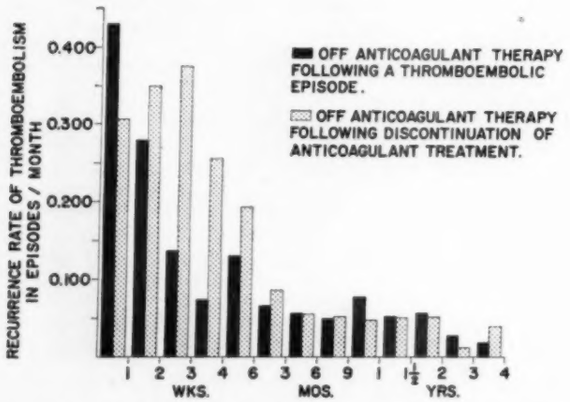


FIG. 3. Comparison of the time-course of the recurrence rate of thromboembolism in patients off anticoagulant therapy after a previous thromboembolic episode and following discontinuation of anticoagulant treatment. Based on the records of ninety patients.

The recurrence rate during anticoagulant treatment, indicated by the hatched blocks, followed roughly a similar pattern, although, as would be expected, at a much lower level during most time intervals.

In Figure 3 the recurrence rate during various time intervals after discontinuation of anticoagulants, as represented by the dotted blocks, is compared with the recurrence rate in patients off treatment following a thromboembolic episode. With the exception of the first week the rate during the first month after stopping therapy was much higher than the rate of recurrence following a previous episode when the patient was without anticoagulant treatment. The same was true to a lesser extent for a period up to six weeks. The lack of the same trend during the first week is not surprising, as on the one hand this is when the rate of recurrence after an episode is highest, and on the other, the anticoagulants still exhibit some effect at least during the first few days after cessation of administration.

Statistical analysis revealed that the difference between the recurrence rate in patients off anticoagulant therapy following an episode and that after stopping anticoagulants is significant at the 5 per cent level (chi-square = 4.051) for the period from the seventh day to the end of six weeks. Furthermore, the increased tendency to recurrent thromboembolism following discontinuation of anticoagulant drugs was evident to approximately the same extent in patients who experienced a thromboembolic episode within six weeks before stopping therapy and in those who had no episodes within six weeks or even three months before discontinuation of treatment.

This danger of recurrence of thromboembolism shortly after stopping anticoagulant therapy appeared to affect to a greater degree those patients who generally exhibited a strong tendency to recurrent episodes while off anticoagulant treatment. The over-all rate of recurrence in patients off treatment was approximately three times higher in those patients who had an episode within six weeks after stopping anticoagulants than in those who did not. The incidence of congestive heart failure was approximately twice as high in patients who experienced thromboembolism shortly after stopping therapy, when compared with those who did not, although this difference was not statistically significant.

The separate analysis of the rates in the groups with rheumatic heart disease, arteriosclerotic and/or hypertensive heart disease and the patients with miscellaneous diagnoses revealed trends similar to those illustrated for the entire group of ninety patients in Figures 2 and 3.

COMMENTS

Application of statistical analysis to the records of this group of patients with thromboembolic phenomena confirmed previous clinical reports [*1–4*] of a marked reduction in the recurrence rate of thromboembolism while the patients were receiving anticoagulants. Although a statistically significant effect was usually not demonstrable by the chi-square test in individual patients until they received anticoagulants for at least two years and/or exhibited a strong tendency to recurrent thromboembolism while off therapy, in about 80 per cent of patients benefit was apparent when a less rigid test (sign test) was applied. This simply indicates that a longer period of observation on anticoagulant therapy is necessary before a long-term effect for an individual patient may be demonstrated by means of the chi-square test.

The small percentage of patients who "broke through" the anticoagulant therapy consistently was made up of those with marked impairment of cardiac function evidenced by the presence of congestive heart failure, atrial fibrillation, double mitral lesions and other complications.

The comparison of all the patients who had had no thromboembolic episodes while receiving anticoagulants with those who experienced at least one episode while on therapy revealed a significantly higher incidence of congestive heart failure in the latter group. The incidence of other complications such as atrial fibrillation, myocardial infarction, double mitral lesion and involvement of other heart valves was also higher in the group with episodes while on anticoagulants although the differences were not statistically significant. It appears, therefore, that thromboembolism is more likely to occur during anticoagulant therapy in patients with marked impairment of cardiac function than in those without marked impairment.

When the rates of recurrence of thromboembolic episodes per month were compared in patients with and without congestive heart failure, there was no difference during the periods they were off anticoagulant therapy. This indicates that, by the nature of the sample, both groups are prone to thromboembolism to the same degree. During anticoagulant therapy there was a marked reduction in the rate of recurrence in the group having no evidence of congestive heart failure. In the group with congestive heart failure there was also a marked reduction in the recurrence rate of thromboembolism during anticoagulant therapy. However, the rate was significantly higher in this group of patients than in the group not in congestive failure. While, numerically, pulmonary emboli were reduced during therapy, they accounted for the largest proportion of the total number of thromboembolic episodes in both groups. The difficulty in differential diagnosis of pulmonary emboli as compared to that of systemic emboli could possibly explain this finding.

With the few exceptions discussed, most patients seemed to benefit from anticoagulant therapy. The majority of the group, however, had had at least two thromboembolic episodes while off treatment. The problem of the therapeutic approach to patients who have had only one thromboembolic episode is more difficult. In the report of Daley et al. [*5*], about two-thirds of the patients with systemic embolism due to rheumatic heart disease had multiple emboli. This study, however, did not include pulmonary emboli, which contribute considerably to the over-all mortality and morbidity from embolism in patients with rheumatic heart disease [*6*]. Furthermore, 33 per cent of the patients who survived the first thromboembolic episode in that study died eventually of an embolic death. This suggests that it might be justifiable to place all patients with one embolic episode due to rheumatic heart disease on long-term anticoagulant therapy, at least until their hemodynamic status can be corrected by surgery [*7*]. That anticoagulant therapy cannot always be discontinued after surgery is evident from the number of emboli which occur associated with, or at any time after, surgery for rheumatic heart disease. It would be desirable to have additional studies, not retrospective in nature, before a final decision can be reached as to whether or not patients with one embolic episode should be placed on long-term therapy. In addition, in some patients long-term anticoagulant treatment may not be feasible or advisable because of relative medical contraindications, lack of cooperation or the absence of proper laboratory facilities.

The present study revealed that the danger of recurrent thromboembolism is highest shortly after a previous episode and diminishes with time, reaching an approximately steady level after the first six weeks. This is in agreement with the data of Daley et al. [*5*] who reported that approximately equal numbers of emboli occurred during the first week, and during the periods one week to one month, one month to six months, six months to one year, etc., after a previous episode. Furthermore, similar findings have been reported with relation to thromboembolism following myocardial infarction [*8,9*].

The actual values of the recurrence rate obtained in the present study may not apply to the general population of patients with a first thromboembolic episode because they are based on a group which does not include patients without cerebral thromboembolism and which is characterized by a large proportion of patients with a strong tendency to recurrent thromboembolism. However, in view of the high percentage of patients with multiple embolism reported by Daley et al. [*5*], it is likely that a large proportion of recurrences might be prevented by a short course of anticoagulant

therapy, similar to that given to patients with acute myocardial infarction. It is suggested, therefore, that all patients with one well documented embolic episode due to rheumatic heart disease, whether or not they are placed on long-term therapy, be given a six weeks' course of anticoagulants. The decision as to whether or not long-term therapy should be continued can be deferred while the patient is evaluated during the initial six weeks. A similar approach should probably be used in patients with embolism associated with other conditions such as fibrillating heart due to any cause.

Another important finding of the present report is the statistical demonstration of increased tendency to recurrent thromboembolism following discontinuation of anticoagulant therapy. It has been stated before that there may be an increase in certain blood clotting factors after anticoagulants are stopped [*10*]. It has also been the impression of many clinicians that a "rebound" phenomenon may follow cessation of anticoagulant treatment [*11*]. The present study strongly suggests this. Furthermore, it appears that the increased danger after stopping the treatment exists whether a thromboembolic episode has occurred in the recent past or not. Six patients in this group who had been receiving treatment without any thromboembolic complications for fifteen to sixty-two months had a recurrence within three weeks after stopping therapy. The tendency to rebound seems to be more pronounced in those with a generally strong tendency to recurrent thromboembolism and in those with congestive heart failure. Although it has not been established that such a procedure is of benefit, it is possible that reduction of the daily dose of anticoagulants by small fractions every few days over a period of a few weeks whenever the anticoagulants are discontinued may decrease the risk of the rebound phenomenon. This was suggested previously by Cosgriff [*2*] but no data have thus far been presented to establish its value.

SUMMARY AND CONCLUSIONS

1. Statistical analysis revealed that the recurrence rate of thromboembolism was significantly reduced by anticoagulant therapy in a group of patients with thromboembolism due to various causes.

2. Although in individual patients a statistically significant effect from treatment using the chi-square test was usually not brought out until they received anticoagulants for at least two years and/or exhibited a strong tendency to recurrent thromboembolism, in about 80 per cent of patients benefit was apparent when a less rigid test (sign test) was applied. This simply indicates that a longer period of observation of patients on treatment is necessary before a long-term effect may be demonstrated by means of the chi-square test for individual patients.

3. The patients who did experience thromboembolism during anticoagulant therapy appeared to be in a more advanced stage of their disease, as indicated by a high incidence of congestive heart failure, atrial fibrillation, myocardial infarction, double mitral lesion and involvement of other valves.

4. Although the rate of recurrence of thromboembolism was equal in patients with and without congestive heart failure during the periods they were off therapy, patients with failure had reduced but relatively higher rates during anticoagulant treatment than did those without failure.

5. The danger of recurrence of thromboembolism was greatest immediately after an episode had occurred and decreased with time. The first six weeks were the most dangerous period. Little decrease was apparent after the first six weeks.

6. It is recommended that patients with thromboembolism, whether placed on long-term therapy or not, should be given a six weeks' course of anticoagulants following a thromboembolic episode.

7. There was an increased tendency to thromboembolism within six weeks after stopping anticoagulants. This was not related to the occurrence of thromboembolism prior to stopping the therapy.

8. When anticoagulants are to be discontinued and the situation permits, the prothrombin time should be lowered gradually and carefully over a period of a few weeks. This recommendation will require modification under certain circumstances, such as hemorrhage or emergency surgery.

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Nodular Panniculitis after Massive Prednisone Therapy*

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IT has been suggested by Greenman et al. [*1*] and by others [*2,3*] that early treatment of rheumatic carditis with relatively large doses of steroid hormones for prolonged periods may reduce the eventual incidence of permanent cardiac damage. The availability of prednisone, a cortisone analogue with high anti-inflammatory but low sodium-retaining activity, has made such treatment easier to administer to patients with rheumatic carditis and congestive heart failure. While trying to evaluate the effects on rheumatic carditis of prolonged therapy with large doses of prednisone, we observed three patients in whom a nodular panniculitis developed after administration of the drug was stopped. The nodules were differentiated clinically and histologically from rheumatic nodules but were similar to the lesions of nodular, febrile, relapsing, non-suppurative panniculitis (Weber-Christian syndrome), and to a lesser extent to those of erythema nodosum. In two patients the panniculitis was mild and resolved spontaneously. In one, the severity of the symptoms twice prompted reinstitution of prednisone therapy, which was followed in both instances by dramatic improvement.

Five patients similar to these have been described by Smith and Good [*4*]. In their patients also a panniculitis occurred when prednisone administration was stopped following its prolonged use in high dosage, and the succession of events observed in both series suggests that the syndrome to be described may have been causally related to the previous administration of prednisone. In Smith and Good's series, treatment with prednisone was not resumed after the nodules appeared. One of their patients died and autopsy revealed widespread lesions in adipose tissue essentially similar to those in the subcutaneous tissue. Another of their patients was being treated for leukemia rather than rheumatic fever, hence the syndrome is probably not uniquely associated with rheumatic fever.

This report consists of detailed descriptions of six episodes of nodular panniculitis in three patients. Its purposes are to stress another possible complication of steroid therapy, to stimulate interest in the study of its mechanism, and tentatively to suggest a way of treating it.

CASE 1. C. H., a seven year old Negro girl, was admitted to Irvington House on December 21, 1955. She was said by the referring hospital to have had rheumatic heart disease since the age of three and had been repeatedly hospitalized for bouts of congestive heart failure and auricular fibrillation.

Four months before admission evidence of congestive heart failure again developed and she was treated in another hospital with a low salt diet, digitalis and mercurial diuretics. At the time of her transfer to Irvington House for continued observation and treatment the heart was markedly enlarged and a long, loud, systolic murmur and a rumbling diastolic murmur were present at the apex. The liver was enlarged and hepatojugular reflux was present. There was 1 plus albuminuria which disappeared shortly after admission. There was no unusual urinary sediment. The hematocrit was 46 per cent and the white blood cell count was 12,100 per cu. mm. Throat cultures were negative for beta hemolytic streptococci and the antistreptolysin O titer was less than 50. The C-reactive protein test [*5*] was negative and the erythrocyte sedimentation rate was 10 (Wintrobe, corrected). A chest x-ray showed considerable en-

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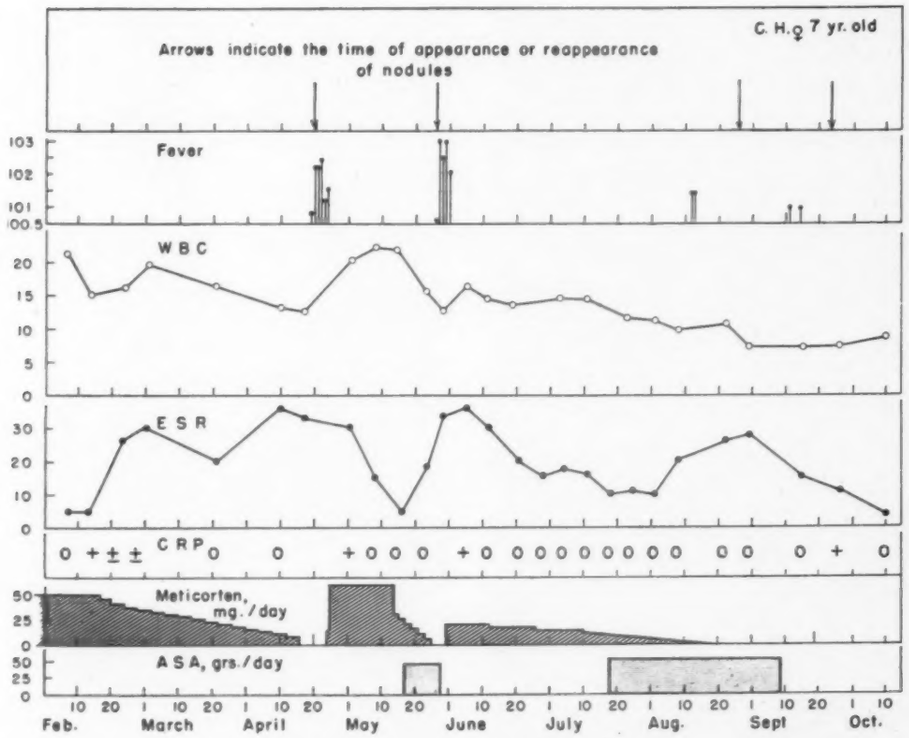


FIG. 1. Case 1. Clinical and laboratory features during withdrawals and reinstitutions of prednisone treatment.

largement of the heart and moderate pulmonary congestion.

Control of the patient's congestive heart failure was difficult with the standard treatment of bed rest, low salt diet, digitalis and mercurial diuretics. Because congestive heart failure in children with rheumatic heart disease is usually a manifestation of rheumatic carditis [*6*], an attempt to suppress the inflammation with prednisone* therapy was undertaken.

During a two month period of treatment with 50 mg. of prednisone per day there was no definite change in the patient's cardiac status. Her weight increased from 40¾ pounds to 73 pounds, with Cushingoid distribution of fat. Gradual reduction of the prednisone dosage was started on February 17, 1956, when a transient glycosuria was detected and a fasting blood sugar of 144 mg. per cent was obtained. Some clinical and laboratory features of the patient's course are illustrated in Figure 1.

Four days after prednisone administration was discontinued the patient's temperature rose to 102.2°F. and two tender, indurated areas were noticed in the subcutaneous tissue of the left arm, where she had been injured recently. During the following two days the fever persisted and many more circumscribed, firm, tender, warm, red nodules appeared over both arms and the posterior thorax. They ranged from 0.5 to 4 cm. in diameter. Most were pruritic, some had an urticarial appearance, and a small vesicle was observed over one.

At this time the patient showed increasing congestive heart failure, and digitalis, which had been stopped eleven days previously because of the appearance of auricular fibrillation, was started again despite the persistence of the arrhythmia.

During the following days new nodules continued to appear while the original ones were decreasing in size. The color of the skin overlying some lesions assumed a bluish hue while it reverted to normal over others. Nodules appeared for the first time over the lower extremities on May 25, ten days after prednisone had been discontinued. The patient was extremely uncomfortable because of generalized pruritus and pain. The nodules, as well as the normal skin between the nodules, were exquisitely tender. Later that day the patient became severely dyspneic with a respiratory rate between 50 and 60, while the heart rate was approximately 90 and the lung fields were clear on physical examination. The patient's condition was critical; she was placed in an oxygen tent and prednisone therapy (60 mg./day) was started again. She also received 1,200,000 units of penicillin and 0.5 gm. of streptomycin daily for six days. Within twelve hours after prednisone administration was reinsti-

* The prednisone used in this study was supplied as meticorten through the courtesy of Dr. J. Black, Division of Clinical Research, Schering Co., Bloomfield, New Jersey.

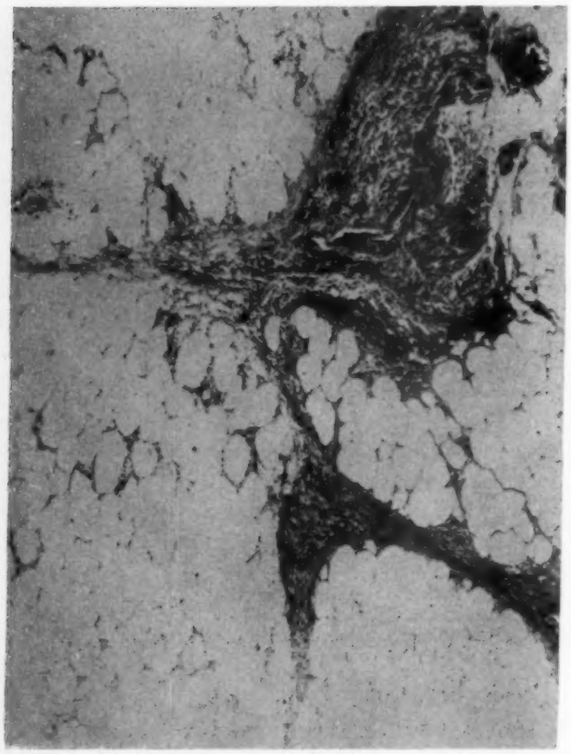


FIG. 2. Case 1. Acute panniculitis. Low power photograph. The first biopsy specimen from patient C. H. Nodule about one week old. Clusters of inflammatory cells separate adjacent fat cells.



FIG. 3. Case 1. Acute panniculitis. High power photograph. The first biopsy specimen from patient C. H. The inflammatory cells are chiefly histiocytes with some neutrophils. Some of the histiocytes have foamy cytoplasm, suggesting the presence of phagocytised fat.

tuted, fever and dyspnea had subsided, the itching had disappeared and the inflammatory changes around the nodules had decreased strikingly.

A biopsy of a nodule on the right forearm was performed twelve hours after the resumption of prednisone therapy. Histologically, the nodules consisted of fibroadipose tissue. There were many small aggregates of histiocytes, foam cells, and a few polymorphonuclear neutrophils in the interstices between fat cells. (Figs. 2 and 3.) A small mass of material resembling fibrinoid contained a few histiocytes. A single vein wall was infiltrated by histiocytes and its lumen contained a minute, organizing thrombus. (Fig. 4.) In general, the inflammation was confined to the fat lobules, while the interlobular septums were spared. Several very small arteries present in the section were within normal limits.

The patient received 60 mg. of prednisone/day for eighteen days until May 14, when the daily dosage was reduced to 30 mg./day. It was then further reduced by 5 mg. every two days. During this period most of the subcutaneous nodules disappeared with the exception of the largest ones, which however became smaller. The administration of 3 gm./day of aspirin was started when prednisone had been reduced to 20 mg./day. This was done in an attempt to avoid possible recurrence of the previously encountered reaction. However, the fever reappeared when prednisone was discontinued. During the next two days tender, hot, red, pruritic subcutaneous nodules reappeared in the same regions as previously, and the few nodules that had not completely disappeared during prednisone administration became larger and inflamed again. The fever persisted and the congestive heart failure worsened. Aspirin was discontinued because of gastric irritation and administration of 20 mg./day of prednisone was started the following day. The temperature then fell to normal and the congestive heart failure subsided. The nodules became less painful and gradually disappeared. After two weeks, a very slow reduction of prednisone dosage was begun.

On July 13, a biopsy of one of the residual nodules on the left arm (now presumably about seven weeks old) was performed. Again, panniculitis was found, confined to the adipose lobules and sparing the interlobular septums. Although the distribution of inflammation was the same as in the first biopsy, its character was quite different; this time there was frank necrosis of fat and the inflammatory cells were histiocytes and giant cells. (Fig. 5.) Some of the latter surrounded clefts resembling those produced by fatty acid crystals. (Fig. 6.)

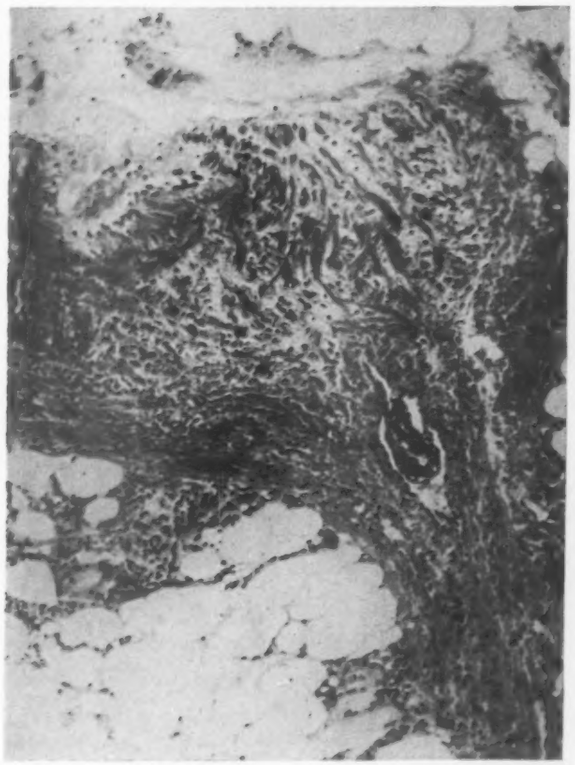


FIG. 4. Case 1. Phlebitis and thrombosis. Low power photograph. The first biopsy specimen from patient C. H. This was the only example of vascular inflammation found in our study. Scattered histiocytes are seen in the vein wall, and a thrombus, just beginning to organize, occupies the lumen. As was true in all of our biopsies, the degree of inflammation among the fat cells surrounding this septal vein is obviously greater than that in the septum.

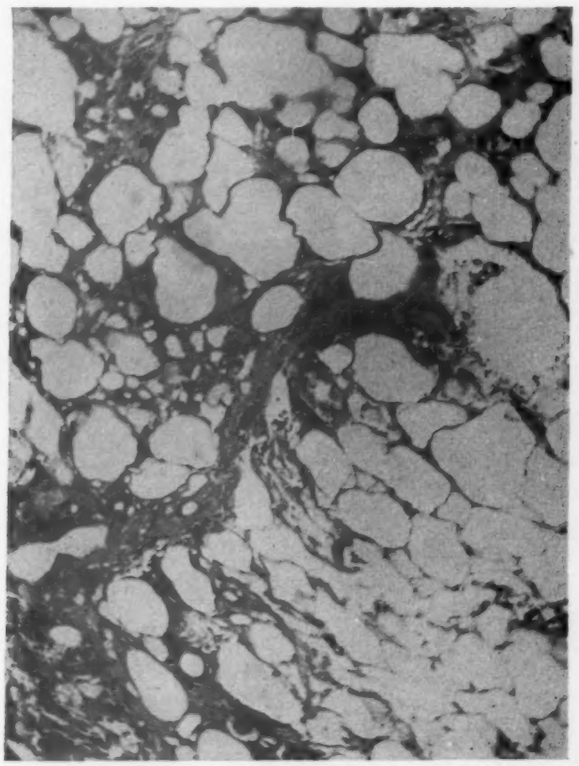


FIG. 5. Case 1. Subacute panniculitis. Low power photograph. Second biopsy specimen from patient C. H. Nodule about seven weeks old. The adipose cells in the lower right portion of the field are entirely necrotic; they are surrounded by a granulomatous inflammatory reaction, including foreign body giant cells and histiocytes, some of which are vacuolated.

Four weeks before the planned termination of prednisone therapy daily administration of 3 gm. of aspirin was started. Prednisone was discontinued on August 14 while aspirin administration was continued. Eight days later dyspnea and pretibial edema were noted and after three more days the patient had a painful, tender left calf. Although no nodules were noted in that area, several new, small, tender nodules appeared on both upper extremities. During this episode the patient was maintained on bed rest, digitalis and aspirin only. The dyspnea and edema cleared rapidly while the nodules became less tender and then decreased in size.

The aspirin was stopped on September 9. Six days later chest pain and monoarticular arthralgia occurred, and after six more days an increased number of pea-sized nodules were noticed evenly distributed over the whole outer surface of the patient's upper arms and on the cheeks.

On October 1, a biopsy was performed of one of the nodules and of the adjacent skin. Histologically, this nodule was virtually identical with the second one biopsied. The skin appeared normal. The nodules persisted through the months of October and November, but were no longer tender. The skin overlying them was pigmented. The nodules, with the exception of two in the deltoid region, disappeared gradually over the next two months while the patient's heart failure remained well controlled.

Comment: After prednisone was discontinued the first time the intense pain, pruritus, high fever and congestive heart failure, unrelieved by digitalis, presented a serious therapeutic problem. Reinstitution of prednisone therapy was followed by dramatic improvement. When prednisone was discontinued the second time the same syndrome occurred with equal intensity and responded equally well to prednisone, administered this time in lower dosage. Withdrawal of prednisone was then effected very gradually. Panniculitis occurred again, but in a much milder form. Administration of aspirin did not prevent the occurrence of the syndrome.

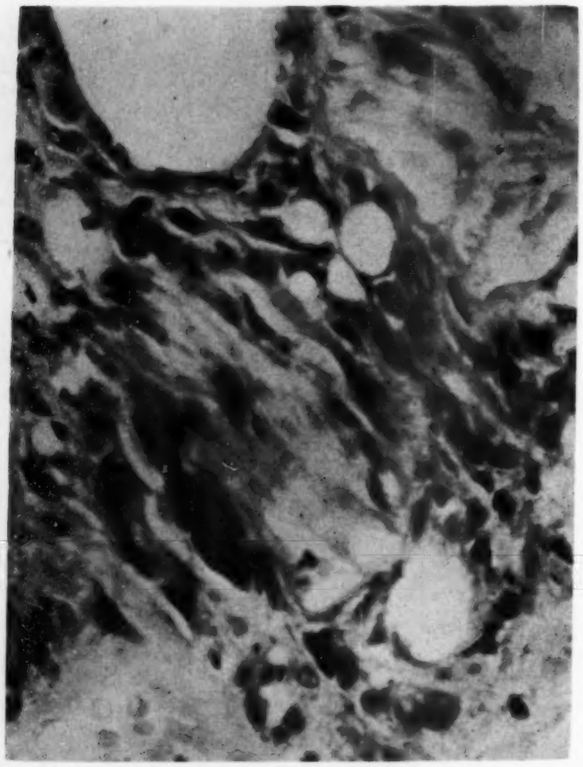


FIG. 6. Case I. Subacute panniculitis. High power photograph. Second biopsy specimen from patient C. H. The giant cell in the center of the field contains clefts which probably represent fatty acid crystals dissolved out during processing of the section. The cells with small vacuoles are histiocytes which have ingested lipid released by necrotic adipose cells.

CASE II. A. R., an eleven year old Puerto Rican boy was admitted to Irvington House for treatment of his third attack of rheumatic fever. During his second attack, in April, 1953, a diagnosis of rheumatic heart disease was made. In November, 1955, he was examined at another clinic because of polyarthritis. Generalized cardiac enlargement, loud apical systolic and diastolic murmurs, anemia and an elevated erythrocyte sedimentation rate were found.

On admission to Irvington House on December 9, 1955, the cardiac findings were as described. Hematocrit was 34 per cent; white blood cell count, 5,000 per cu. mm., urinalysis, negative. The test for C-reactive protein was positive (1 plus) and erythrocyte sedimentation rate was 30 mm./hour. The antistreptolysin O titer was 625 units/cc. An x-ray film revealed over-all cardiac enlargement.

Shortly after admission a sinus tachycardia developed and the patient's liver became tender and enlarged. The venous pressure was elevated. These findings of congestive heart failure, associated with a recent history of arthritis, and laboratory evidence of recent streptococcal infection, were considered indicative of active rheumatic carditis.

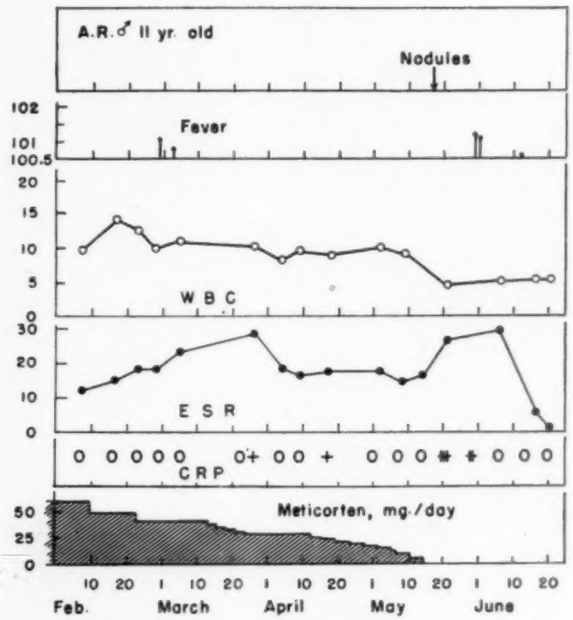


FIG. 7. Case II. Clinical and laboratory features during and after withdrawal of prednisone treatment.

Treatment with 60 mg./day of prednisone was started on December 20, 1955. The clinical signs of congestive heart failure gradually subsided. The patient's weight rose from 73 pounds to 106¾ pounds, with a Cushingoid distribution of fat. Tapering of prednisone was started on February 9, 1956, but when the daily dosage was reduced to 32.5 mg./day congestive heart failure reappeared. The patient was digitalized; the same dose of prednisone was maintained. Congestive heart failure was fully controlled by the end of March, and tapering of prednisone was then resumed. Some clinical and laboratory features of the patient's course are illustrated in Figure 7.

Two days after the completion of prednisone therapy numerous tender, mildly pruritic subcutaneous nodules measuring up to 1.5 cm. in diameter were noticed over the anterior thorax, back and proximal extremities. Several larger, non-tender nodules were also felt in the patient's cheeks. The skin overlying all of them was normal. A biopsy of one of the nodules performed on May 25, 1956, revealed numerous foci of interstitial inflammation chiefly between fat cells in the subcutaneous fibroadipose tissue. Most of the inflammatory cells were histiocytes, lymphocytes and neutrophils. There was an area of acute fat necrosis. (Fig. 8.) No angiitis was observed.

Digitalis was discontinued on June 4 without reappearance of congestive heart failure. Convalescence was then uneventful.

Comment: Although the total amount of prednisone administered (5,649 mg.) was larger than in the first course of treatment in Case I (4,607.5 mg.) the panniculitis which followed treatment

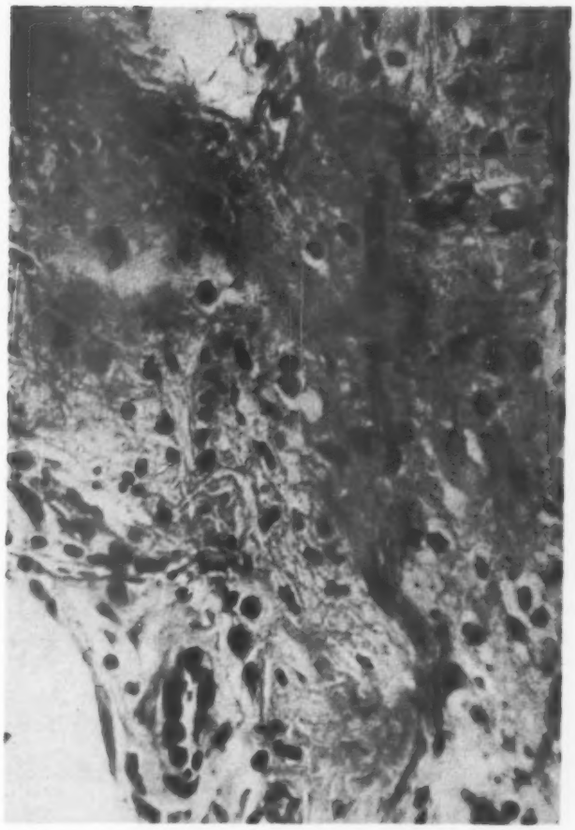


FIG. 8. Case II, patient A. R. Acute panniculitis. High power photograph. Nodule about a week old. Histiocytes, neutrophils, cellular debris and clefts left by fatty acid crystals are seen in an area of acute fat necrosis.

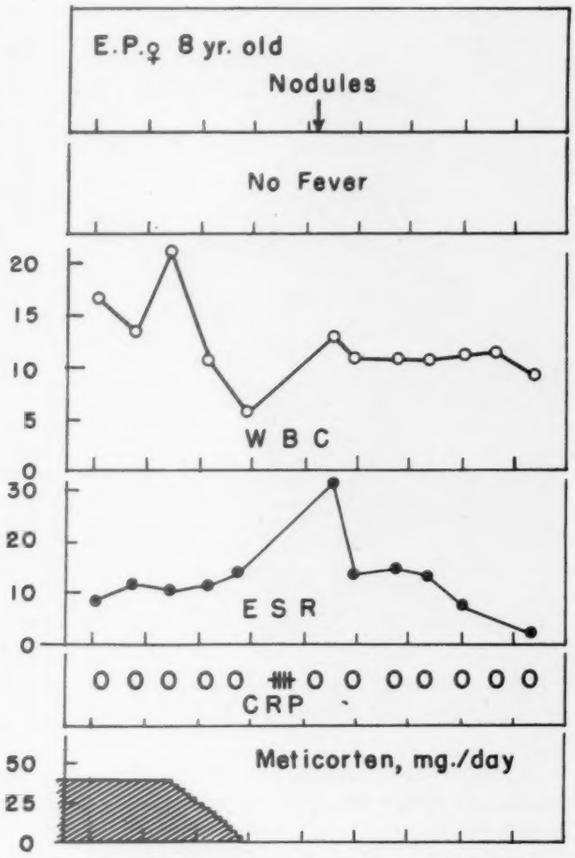


FIG. 9. Case III. Clinical and laboratory features during and after withdrawal of prednisone treatment.

was milder. The greater age of the patient, the smaller over-all physiological effect of the drug, as suggested by the less striking weight increase, and the slower tapering of the drug may all be relevant factors in this connection.

CASE III. E. P., an eight-year old girl of Puerto Rican extraction, was admitted to Irvington House on April 13, 1956. The preceding December she had complained of poor appetite and fatigability on exertion. She was admitted to another hospital on March 2, 1956, complaining of joint pains. Fever, tachycardia and a loud apical systolic murmur were present. The C-reactive protein test was positive, the erythrocyte sedimentation rate was elevated, and the antistreptolysin O titer was 833 units/cc.

The patient received aspirin for one day only. Four days later, daily administration of 60 mg. of prednisone was started with complete suppression of symptoms within four days. This dosage was maintained for fourteen days, then reduced to 40 mg./day and stopped after eighteen more days.

On admission to Irvington House the patient had a Cushingoid appearance. A loud systolic murmur and a rumbling diastolic (the latter present only after exercise) were heard at the apex. The hematocrit was 40 per cent; the erythrocyte sedimentation rate, 12 mm., the white blood cell count, 12,700 per cu. mm.; and the C-reactive protein test was positive (2 plus). Throat culture was negative for group A streptococci and antistreptolysin O titer was 100 units/cc.

Steroid therapy had been discontinued five days prior to transfer. Because the patient had a rapid pulse rate and the C-reactive protein test was positive, rheumatic carditis was considered to be still active. Therapy with 40 mg./day of prednisone was reinstituted immediately and after eleven days of treatment all clinical and laboratory signs of rheumatic activity subsided. Prednisone dosage was reduced by 2.5 mg./day after a month of therapy and discontinued entirely fifteen days later. During this period the apical diastolic murmur disappeared. The patient's weight rose from 56½ pounds to 74½ pounds. Certain clinical and laboratory features of the patient's course are illustrated in Figure 9.

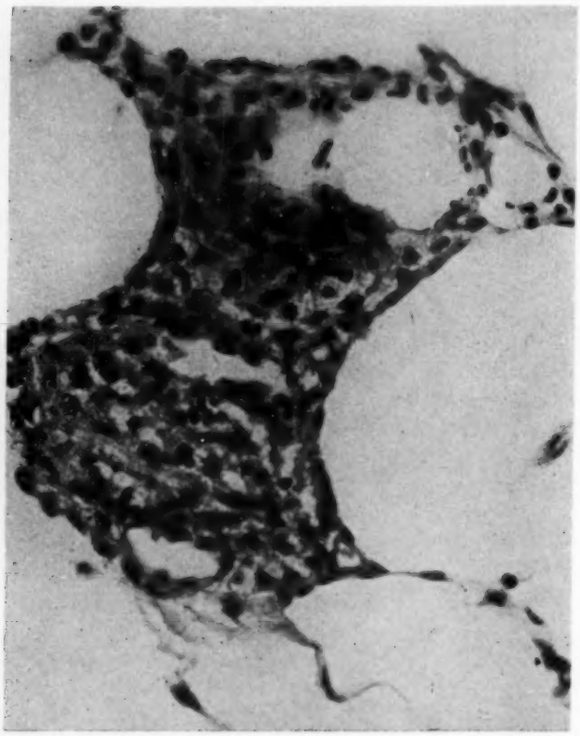


FIG. 10. Case III, patient E. P. Acute panniculitis. High power photograph. Nodule about four days old. Similar to Figure 3, but neutrophils are more numerous in this earlier biopsy.

Twelve days after prednisone administration had been stopped a transient arthralgia developed and itching nodules appeared on her cheeks and arms. These were firm, slightly raised and surrounded by irregular brownish areas of pigmentation.

A biopsy of a subcutaneous nodule was performed four days after it had been noticed. This revealed aggregates of mononuclear cells and neutrophils between fat cells of the subcutaneous adipose tissue. (Fig. 10.) No angiitis or necrosis was found.

The nodules began to disappear in about a week and no new ones were detected. Following this episode the patient's convalescent course was uneventful.

Comment: This patient received a smaller total dose of prednisone (3,140 mg.) than the other two. Her panniculitis was mild, no fever appeared, and the whole episode could have been overlooked in the absence of close medical supervision.

COMMENTS

It is well known that manifestations of disease activity may reappear at the end of suppressive therapy for rheumatic fever [*7,8*]. In some cases these manifestations are unmistakably rheumatic (i.e. migratory polyarthritis, endocarditis) and it is logical to assume that they are expressions of the initial rheumatic process. More frequently, the manifestations of disease activity which appear after therapy is stopped are non-specific (i.e., fever, tachycardia, elevated erythrocyte sedimentation rate) and are thus compatible with, but not characteristic of, rheumatic fever. The cases presented herein illustrate a third type of post-treatment abnormality, whose features were unrelated to rheumatic fever as hitherto described.

TABLE I

HISTORIES OF PATIENTS WITH NODULAR PANNICULITIS AFTER PREDNISONE THERAPY

Patient	Sex and Age (yr.)	History of Rheumatic Fever or Presence of Rheumatic Heart Disease	Prednisone Received (mg.)	Duration of Prednisone Administration (days)	Weight Change during Therapy (lb.)
C. H. (1)	F, 7	+	4,607.5	89	40¾ to 73
(2)	.....	..	1,230	30	65 to 79
(3)	.....	..	1,074	79	No gain
(4)	.....	..	.....	...	.....
A. R.	M, 11	+	5,649	146	73 to 106¾
E. P.	F, 8	+	3,140	79	56½ to 79½*

NOTE: C. H. (1), (2), (3) and (4) in this table and in others refer to the successive episodes of panniculitis observed in the same patient.

* During the last forty-seven days of therapy; the initial weight of the patient is not available.

The natural history of this syndrome, as observed in the patients here presented, may be summarized as follows. All the patients had received a long course of relatively high doses of prednisone for the treatment of rheumatic carditis. (Table I.) One to thirteen days after discontinuation of prednisone, subcutaneous nodules appeared. Cheeks, arms and trunk were the sites most commonly involved. In some instances, the skin overlying the nodules was red and warm, while in others it was normal. The nodules were firm, ranging in diameter from 0.5 to 4.0 cm., and in most cases they were pruritic and tender. (Table II.) In the first two episodes in Case I the patient suffered intense pain and pruritus. When prednisone administration was reinstituted, striking subjective and objective improvement was noticed. In the instances in which the panniculitis was mild the nodules disapeared spontaneously over a period of months, leaving behind an area of skin pigmentation.

During some of the episodes, fever, joint pains

TABLE II
DESCRIPTION OF NODULES

Patient	Interval between End of Therapy and Appearance of Nodules (days)	Location of Nodules	Diameter of Nodules (cm.)	Pruritus	Tenderness	Residual Pigmentation
C. H. (1)	4	All limbs, chest	0.5–4	+	++	+
(2)	1	All limbs, chest	0.5–4	+	++	+
(3)	11	All limbs, chest	0.5–1	+	+	+
(4)	..	Upper arms, cheeks	0.5	−	±	+
A. R.	2	Arms, chest, cheeks	0.5–2	±	±	+
E. P.	13	Arms, cheeks	0.5–1	+	−	+

and heart failure occurred at approximately the time the nodules appeared. (Table III.) Non-specific laboratory tests for inflammation were usually positive. The elevated white blood cell count may have been related to the preceding administration of prednisone. (Fig. 1.)

TABLE III
ASSOCIATED FINDINGS

Patient	Fever	Joint Pains	Heart Failure	Erythrocyte Sedimentation Rate Elevation	C-Reactive Protein Test	White Blood Cell Count	Response to Prednisone
C. H. (1)	+	−	+	+	+	Elevated	+
(2)	+	−	+	+	+	Elevated	+
(3)	±	+	+	+	−	Elevated	..
(4)	±	−	−	−	+	Normal	..
A. R.	±	−	−	+	+	Normal	..
E. P.	−	+	−	+	+	Elevated	..

Histological study of the biopsy specimens from all three patients showed acute (Figs. 2, 3, 8 and 10) or subacute (Figs. 5 and 6) inflammation of the panniculus. The type of inflammatory cells changed with the age of the lesions: they were predominantly neutrophils and mononuclear cells in a four day old nodule (Fig. 10), while older nodules showed a greater number of histiocytes and giant cells. Some of the latter surrounded clefts, presumably negative images of fatty acid crystals dissolved out during processing of the section. Several histiocytes had foamy cytoplasm, suggestive of ingestion of fat released by destroyed adipose cells. In all biopsy specimens, the inflammatory cells were noted almost exclusively in the interstices between fat cells within the fat lobules, while the interlobular septums were, for the most part, free of inflammation. The blood vessels were virtually uninvolved. In the entire study only one isolated example of vascular inflammation was found (Fig. 6), a small vein with scattered histiocytes in its wall and an organizing thrombus in its lumen.

Since all our patients had rheumatic carditis and because the syndrome observed occurred after prednisone therapy had been stopped, the possibility that it was a manifestation of rheumatic "rebound" was considered. Fever, laboratory signs of inflammation, arthralgia and exacerbation of heart failure, common findings after the end of therapy in rheumatic fever, were all present in one or more of our cases. The nodules observed in our patients, however, differed from rheumatic nodules both clinically and histologically. Rheumatic nodules are painless, tend to occur over bony surfaces, are not accompanied by inflammation of the overlying skin and on clearing do not leave a pigmented area. (Table IV.) Histologically, they consist of vascular connective tissue, containing foci of fibrinoid degeneration surrounded by histiocytes; the latter are often quite large and resemble Aschoff cells. No inflammation or necrosis of fat is found.

The clinical appearance of the lesions in some of the episodes described resembled that of erythema nodosum, a syndrome once [*9*] but no longer [*10*] considered to be frequently associated with rheumatic fever. The lesions of erythema nodosum, however, have a characteristic distribution over the extensor surfaces of the limbs, which was absent in the patients herein described. Furthermore, unlike the histological picture revealed by our biopsies, in erythema nodosum the fibrous septums within

TABLE IV
DIFFERENTIAL FEATURES OF SUBCUTANEOUS NODULES*

Data	Rheumatic Nodules	Erythema Nodosum	Weber-Christian Syndrome	Nodular Panniculitis after Prednisone
Pruritus	−	−	−	+
Tenderness	−	+	+	+
Redness	−	+	+ or −	+ or −
Gross distribution	Over bony surfaces	Extensor surfaces of limbs	Extremities, trunk	Cheeks, trunk, extremities
Residual skin atrophy	−	−	+	−
Residual pigmentation	−	Occasional	+	+
Site of inflammation within the subcutaneous fat tissue	−	Interlobular septums at least as much as the fat lobules	Fat lobules more than the interlobular septums	Fat lobules more than the interlobular septums

* Typical differential features of rheumatic nodules, erythema nodosum, Weber-Christian syndrome and nodular panniculitis after prednisone therapy. Table compiled from different sources [*6,10–12*] and from the cases presented.

the fat are inflamed, at least as much as the fat tissue itself [*11*].

The disease process observed in our patients presented several similarities to, and some differences from, febrile, nodular, relapsing, nonsuppurative panniculitis, or Weber-Christian syndrome [*12*]. This is a rare syndrome of unknown etiology, characterized by the appearance of tender, subcutaneous nodules, often accompanied or preceded by fever, and other constitutional symptoms. The skin overlying the nodules in Weber-Christian syndrome may be red in the early stages and becomes pigmented later. The nodules may appear on all parts of the body, usually sparing hands, feet and face (the latter was regularly affected in our cases). They heal spontaneously leaving a depressed scar. This was never observed in our patients. Histologically the lesions observed by us suggest those of Weber-Christian syndrome because both show fat necrosis and preferential involvement of fat lobules with sparing of the connective tissue septums. In the present state of our knowledge of the nodular panniculitides it is impossible to assess how significant these similarities and differences actually are. (Table IV.)

These observations as well as those of Smith and Good [*4*] suggest that nodular panniculitis should be added to the list of possible untoward reactions to steroid hormone therapy. It has thus far been reported only in children following the administration of prednisone. Whether it may occur also in adults and whether it may follow the administration of steroids other than prednisone are open questions.

Since all the patients with nodular panniculitis had been treated with large doses of prednisone for long periods, it is probable that the syndrome may be avoided if prednisone is used in smaller doses for shorter periods. However, if the post-prednisone nodular reaction does occur, and its severity threatens the life of the patient, or causes marked discomfort not relieved by non-steroid medication, the sequence of events in our first case suggests that its relief may be achieved by further cautious use of the same drug.

SUMMARY

Six episodes of nodular panniculitis are described. They occurred in three patients after the end of prolonged administration of large doses of prednisone. The relationship of this syndrome to rheumatic "rebound," erythema nodosum and Weber-Christian syndrome is discussed and the possibility of relieving its manifestations by further cautious administration of prednisone is pointed out.

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Reviews

The Pathogenesis of Pulmonary Emphysema*

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"This is not the end. It is not even the beginning of the end. But it is perhaps, the end of the beginning."
Winston Churchill

This paper presents for examination observations and conclusions from which I developed the concept of the pathogenesis of emphysema during a study of its macroscopic and histological features [*1–4*]. The morphological studies which supported this concept were intended to clarify more than the pathogenesis of emphysema; an equally important and interdependent aim was a reconsideration, in broad outline, of the natural history of pulmonary inflammation. In developing this concept, it will be necessary first to consider the normal lung structure.

PRELIMINARY CONSIDERATIONS

Normal Anatomy. The bronchial tree is best regarded as a system of passages dividing dichotomously many times and eventually ending blindly. The walls of the proximal passages (the trachea, bronchi and bronchioles) are complete; those of more distal passages (respiratory bronchioles, alveolar ducts and alveolar sacs) show numerous small diverticula, each a single and separate unit, the alveolus.

In the divisions of orders of respiratory bronchioles, of which there are usually three, progressively more of the wall is represented by an interlacing mesh of musculoelastic tissue forming the mouths of the alveoli until, in the alveolar ducts, nothing remains of the wall other than the open mesh. After one further division they terminate in alveolar sacs. (Fig. 1.) Thus in effect each of these passages is a closed tube, the limits of which are alveolar walls. Adjacent passages are separated by two layers of ultra-thin alveolar epithelium and a little connective tissue

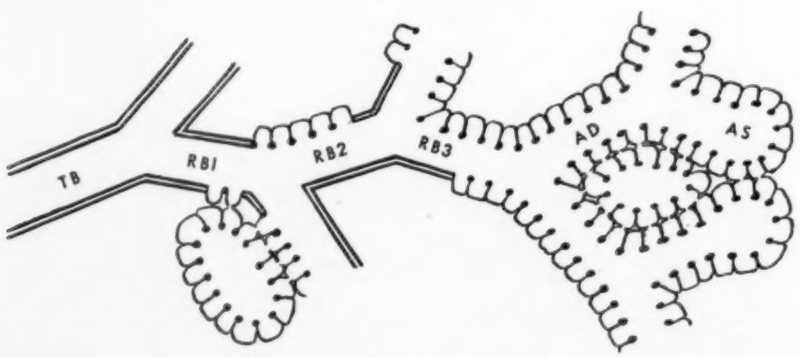


Fig. 1. Diagrammatic representation of the normal divisions of a terminal bronchiole. This shows three divisions of respiratory bronchioles—the most common number. Two passages of adjacent and related systems have been included to show how neighbouring passages, with alveoli in their walls, may communicate freely by means of alveolar pores (Cohn). TB = terminal bronchiole; RB1 = first respiratory bronchiole; RB2 = second respiratory bronchiole; RB3 = third respiratory bronchiole; AD = alveolar duct; AS = alveolar sacs.

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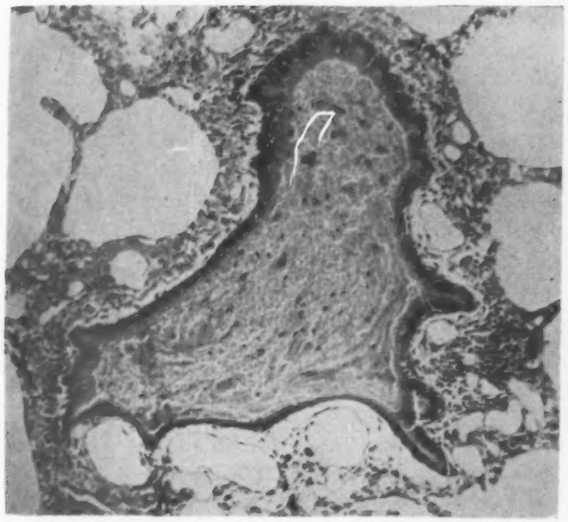


FIG. 2. Photomicrograph showing a small bronchiole containing a plug of mucus. Hematoxylin and eosin, original magnification × 90.

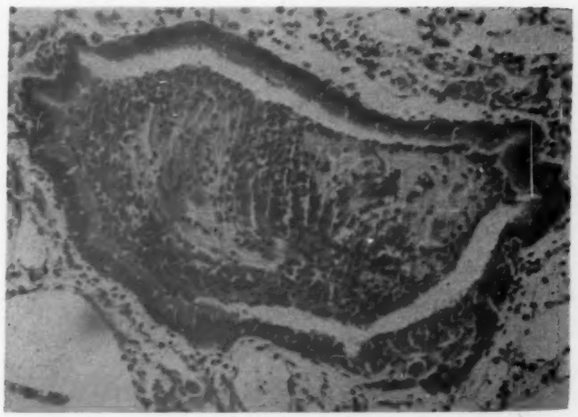


FIG. 3. Photomicrograph of a bronchiole containing a plug of infected mucus. There are wandering cells in the peribronchiolar tissues and numerous polymorphonuclear leukocytes and phagocytes in the mucus. Hematoxylin and eosin, original magnification × 180.

containing capillaries, together with elastic tissue and reticulin fibrils. However, these walls are incomplete, there being small defects or alveolar pores (Cohn), by which adjacent alveoli and, therefore, adjacent passages communicate. These pores are normally too small to be demonstrable in routine 7 microns histological sections so that, in such sections, the walls of the normal alveoli are apparently complete. Morphological and physiological evidence demonstrating the presence of these pores has been discussed previously [*5*].

An important unit of lung tissue is the secondary lobule. This is the smallest unit completely enclosed by septums and occupies 1 to 2 cu. mm. It is supplied by a bronchiole which, after five or six divisions, ends in a number of terminal bronchioles, all situated near the middle of the lobule; their branches supply the remainder of the middle of the lobule, and the periphery in a radial fashion.

Bronchiolitis. The concept of pathogenesis of emphysema required reassessment of the general pathology of bronchiolar inflammation; it has been presented in previous papers [*5,6*]. The homeostatic mechanisms maintaining the patency of the airways were shown to be dependent on the efficiency of cilia, cough and collateral ventilation, patency being constantly threatened by fluids within the tree, particularly by its own secretion—mucus. (Fig. 2.) It was concluded that temporary complete obstruction of small bronchioles by mucus was an everyday event in each of us, but that mucus was rarely aspirated in any quantity beyond the proximal orders of respiratory bronchioles. What material is aspirated into and beyond the respiratory bronchioles is rapidly phagocytosed, the aeration of these passages obviously being maintained during a period of occlusion by collateral ventilation through the alveolar pores. As long as aeration is maintained beyond an occluded bronchiole, coughing ordinarily rapidly expels the plug.

Aspirated material (including mucus) usually contains many bacteria which are constantly entering the lower respiratory tract both in inspired air and in secretion from the nasopharynx. Normally a small proportion of air-borne bacteria is constantly reaching the passages beyond the respiratory bronchioles where they are readily dealt with; on the other hand, most are arrested in more proximal passages and are rapidly expelled along with the secretions, and so produce no damage. However, if infected material remains static within the lumen of an air passage, bacterial growth and proliferation with the stagnant material leads to an acute inflammatory response in the adjacent wall. (Fig. 3.) The site at which such prolonged retention was most commonly found was in the smallest bronchioles, particularly the proximal orders of respiratory bronchioles; it was found with progressively decreasing frequency in the terminal bronchiole and larger bronchioles. Such retention in these passages with subsequent acute bacterial bronchiolitis (Fig. 4) occurs in any circumstance in which the homeostatic mechanisms (ciliary action, cough and collateral ventila-

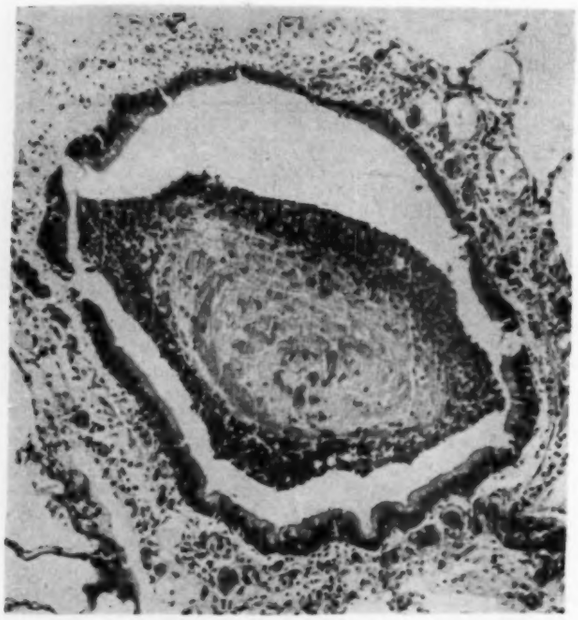


FIG. 4. A small bronchiole showing gross invasion of the mucous plug by wandering cells. The contraction of the plug from the wall is artefact. Hematoxylin and eosin, original magnification × 90.

tion) are ineffective because of factors operating locally or generally.

These factors have been outlined [*5*]; in general they may be classified into two groups: those that produce tissue damage themselves (such as viral infections) and those that do not do so directly, subsequent inflammation being due solely to the complicating bacterial infection (such as occurs with loss of the cough reflex in coma). In any particular case, several disorders of homeostasis can usually be recognized; for instance, during an attack of influenza the homeostatic mechanisms maintaining patency of the bronchial tree are affected by destruction of cilia and also by the excessive amount of secretion (mostly exudate) within the lumen of the bronchial tree. Aspiration of secretions and widespread plugging of small bronchioles is inevitable but, in the active adult with a strong cough and free collateral ventilation of the sequestered regions, prolonged retention of bronchiolar plugs containing bacteria from the nasopharynx does not, as a rule, occur. The bacterial phase of bronchiolitis is evident clinically only by purulent sputum persisting beyond the phase of viral damage. Generally only the more "virulent" organisms, such as Staphylococcus aureus or types I and II pneumococci, can establish infection in such circumstances, and then only because they can grow and proliferate freely in tissues adjacent to the plug. On the other hand, in the elderly, ill patient breathing is shallow and this reduces the collateral ventilation so that, since coughing is weak, bronchioles not only are plugged more frequently but the plugs remain. Even pathogens of low virulence such as green streptococci may attain sufficient concentrations within the plugs to produce an acute bacterial bronchiolitis.

Spread of the inflammatory process depends on several factors including host "tissue resistance" and the nature of the damaging agent as well as on the efficacy of homeostatic mechanisms. The minimal and by far the most common lesion is entirely restricted to the wall of the occluded bronchiole—simple acute bronchiolitis. In these circumstances the plug and therefore the inflammation does not usually extend beyond the proximal orders of respiratory bronchioles, more distal passages remaining aerated. The proximal extent of the plug varies considerably from case to case, one to several bronchiolar divisions being occluded.

Less common exudate is found distal to the respiratory bronchioles. Most often it simply fills the alveoli of some of the passages beyond the plug, leaving the main passage clear. This is seen either in the exudative phase or later, where it represents a stage in the resolution of more extensive lesions, such as bronchopneumonia, in which all passages near a terminal bronchiole are filled with exudate and are consolidated; passages on the periphery of the lobule remain aerated by collateral ventilation. (Fig. 5.) Collateral ventilation depends on the patency of the alveolar pores; if, during the exudative phase, they are occluded by exudate, lobular collapse may occur. Whether collapse or consolidation predominates depends largely on the nature of the damaging process and the efficacy of the homeostatic mechanisms.

Acute inflammation of small bronchioles must therefore be the focal point of attention in inflammatory disease of the lung. (Fig. 6.) All damaging agents produce their maximal effects in this area and there are few disorders of lung function and few pulmonary lesions that are not complicated by pyogenic acute bacterial inflammation of the small bronchioles. Moreover, acute bronchiolitis is an extremely common condition occurring on almost innumerable occasions during the lifetime of each of us.

Another observation which has not previously



FIG. 5. Photomicrograph showing a small bronchiole filled with exudate and a localized area of bronchopneumonia. Adjacent alveoli of this lobule are aerated by collateral ventilation and the proximal spaces are dilated. Elastin stain, original magnification × 30.

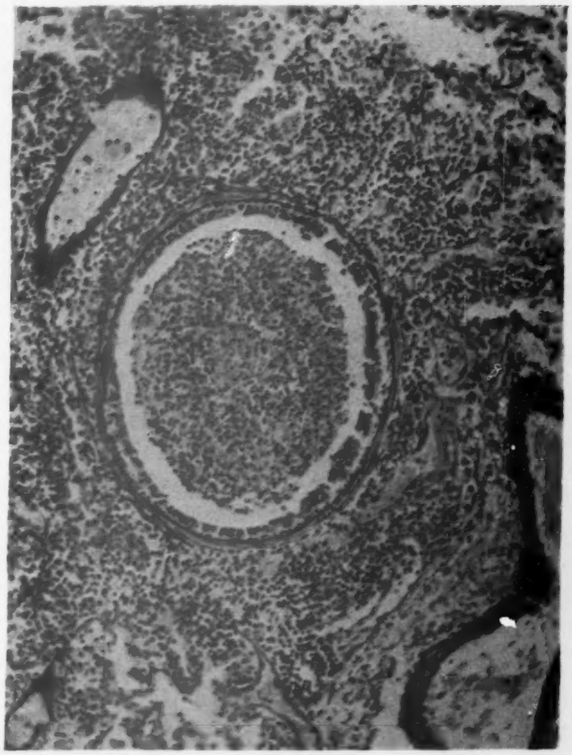


FIG. 6. A small bronchiole filled with infected exudate with infection of the surrounding tissues. The elastic tissue of the wall of the bronchiole is well shown. Elastin stain, original magnification × 90.

been stressed is that resolution of pulmonary inflammation is not as complete as is generally inferred. Residual changes resulting from recurrent respiratory tract infection were found in all adults and were readily demonstrable in the small bronchioles. These changes were maximal in the proximal orders of respiratory bronchioles, with progressively less evidence of damage in the terminal, preterminal and more proximal bronchioles [*6*]. Bronchiolar damage was generally greater in regions in which more distal passages had been involved in the exudative phase and had not become reaerated, leaving what is usually described as "scar," condensed, organized lung tissue. Bronchioles in such regions showed much damage to their walls and many were completely obliterated. Similar bronchiolar wall damage and obliteration, although generally less in extent, were also found in aerated lung. Such lung might have been reaerated following inflammatory involvement or might never have been significantly involved despite the obstruction and inflammation of the supplying bronchiole.

A material conclusion of this part of the study was that some degree of permanent damage and obliteration of the smallest bronchioles can result from the mildest of "upper" respiratory tract infections; in all such infections, although not clinically apparent, it is the smallest bronchioles which are exposed to the most damage. The cumulative effect of such minor episodes eventually becomes functionally significant.

THE PATHOGENESIS OF EMPHYSEMA

The basic structural change in emphysema is dilatation of the air passages distal to the terminal bronchioles and breakdown of their "walls," that is, breakdown both of the tenuous alveolar walls and also the somewhat stronger musculoelastic mesh that outlines the lumen of the main passage. (Fig. 7.) The basic phenomena inducing this change are essentially similar whatever the form of the emphysema; other factors determine the well organized morphological, clinical and physiological variants of the disease.

The factors leading to the early lesions of emphysema are discussed as a sequence of

changes: (A) bronchiolar obstruction, (B) "trapping" of collaterally ventilated air beyond the obstruction, and (C) disruption of the air passages beyond the obstruction.

Bronchiolar Obstruction. During every incident of acute bronchiolitis there is complete obstruction of small bronchioles, which persists at least long enough for the inflammation to become established. Complete obstruction is clearly an integral part of the process.

Subsequently, permanent obliteration of the occluded bronchioles may ensue, particularly if the plug is retained for some time. The phenomenon of permanent obliteration therefore depends at least as much on the efficacy of homeostatic mechanisms acting to expel the plug as on the potential of the damaging agent. It was concluded that obliteration was maximal in the proximal orders of respiratory bronchioles and was progressively less common in larger bronchioles, and beyond the age of forty, obliteration of the smallest bronchioles was relatively extensive and widespread even in lungs having the most normal macroscopic appearance [*6*].

This conclusion is contrary to present views. Direct demonstration of the remnants of obliterated bronchioles was not effected in many cases and the evidence for these conclusions was necessarily to some extent circumstantial. The main evidence was:

Recent Lesions. Study of recent irreversible obliterative changes in bronchioles (lesions which, if sought, are relatively easily identified) confirmed that proximal orders of the respiratory bronchioles were affected much more often than those bronchioles even three or four divisions proximally.

Older Lesions. Older lesions are inconspicuous; in damaged lungs the number of bronchiolar divisions was always less than normal. Even where bronchioles end blindly the obliterated remnants of more distal passages frequently could not be identified. With progressive damage larger bronchioles were found to be obliterated but, in a particular case, only the largest involved could be positively identified. The general observation that obliterated bronchioles eventually become inconspicuous (Fig. 8), if not imperceptible, is readily explicable on several grounds. The more important of these include:

(A) Alterations in architecture: Few tissues show alterations of their structure following inflammatory lesions as readily as the lungs, a



FIG. 7. A localized area of consolidation. The distal part of the bronchiole (in upper part of section) is sharply outlined by elastic tissue. There is some dilatation of proximal alveoli. Elastin stain, original magnification × 20.

characteristic related directly to its peculiar physical form. Positive identification of obliterated bronchioles usually required recognition of the original structure. Even in regions in which damage was slight this was usually impracticable. Only in occasional lesions, and if special attention were paid to this problem, could the original structure be reconstructed with any confidence.

(B) The characteristics of the tissues of the bronchiole: No tissue in the lung was found incapable of regeneration or new formation in appropriate circumstances [*6,7*]. Furthermore it was concluded that "epithelial" and connective tissue cells, given the appropriate stimulus, are interchangeable. In view of these observations, the finding of residual tissue having features suggestive of an origin from an obliterated bronchiole was necessarily assessed cautiously. (Fig. 9.) It was clear moreover that even mature collagen, characteristically present in those old obliterated bronchioles that were positively identified, was frequently resorbed [*3*]. After a short distance residual structures were rarely seen when an obliterated large bronchiole was positively identified and its peripheral distribution traced.

(C) Secondary communications: A further confusing factor was the formation of secondary communications which were of two general types: those found between terminal (and larger)

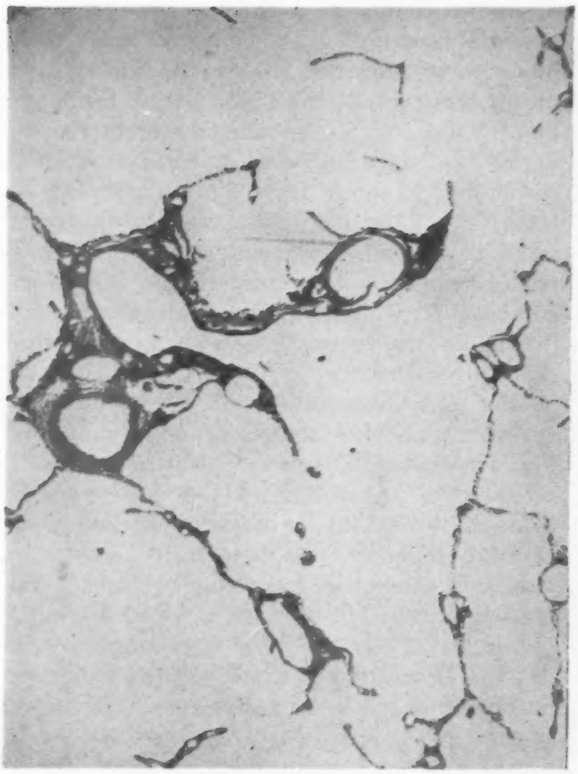


FIG. 8. A terminal bronchiole is opening into grossly dilated alveolar spaces. An organized and inconspicuous scar (representing an obliterated bronchiole) is present between the dilated bronchiole and the vessel. Hematoxylin and eosin, original magnification × 30.



FIG. 9. A bronchiole which is grossly fibrosed. An indication of its original form is given by the surviving layer of elastic tissue; there is a large amount of organizing granulation tissue between this and the epithelium. Elastin stain, original magnification × 90.

bronchioles and adjoining air spaces which were regarded as inflammatory in origin [*6*] and those due to the process of emphysema. In both cases it was necessary to attempt to distinguish these from original passages.

Due to these factors few obliterated small bronchioles were positively identified. In many more cases it could be definitely stated that obliteration had occurred although positive identification was not feasible. Indeed, although recent obliteration of respiratory and terminal bronchioles was commonly found, no old obliteration of terminal or even preterminal bronchioles and their arborizations was ever recognized. Indeed, such recognition was not anticipated. At the same time it was abundantly clear, even on a perfunctory count of bronchiolar branches, that disappearance of these small air tubes was extremely common.

"*Air-Trapping.*" During the exudative phase of acute bronchiolitis the more peripheral passages may remain aerated by collateral ventilation through the alveolar pores; subsequently the infected plug may be expelled or the bronchiole may become permanently obliterated.

The pressures within collaterally ventilated regions, during the respiratory cycle, are not normal. This has been demonstrated in man by Baarsma, Dirken and Huizinga [*8*], in animals by Lindskog and van Allen [*9*] and by Baarsma and Dirken [*10*]. Lindskog and van Allen measured the pressures and found that, during quiet respiration, there was a small constant elevation in air pressure of approximately 1 cm. H_2O which tended to expel a plug completely obstructing a bronchus of a lobe, the lung distal to the plug being maintained by collateral ventilation from an adjoining segment. (It should be noted that in these experiments the air could reach the region beyond the obstruction not only by alveolar pores but also recurrently through the bronchial branches beyond the block). This is a direct physiological demonstration of what is referred to here as "air-trapping." The rise in the average pressure during the respiratory cycle is clearly minimal

in a small collaterally ventilated region surrounded on all sides by normal lung. The degree of air-trapping is increased when the path of collateral ventilation is long and tortuous, that is, when the air must traverse numerous peripheral passages and alveolar walls to reach the region concerned.

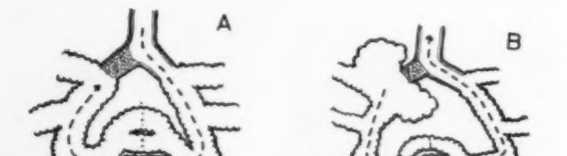


FIG. 10. Drawings to show the effect of obstruction by a plug of a terminal bronchiole. The passages normally aerated by this receive their air from adjacent passages through alveolar pores. During inspiration (A) the air enters easily through dilated passages and enlarged pores. On expiration (B) air escapes readily from the passages of the patent bronchiole but does not pass easily from those of the plugged bronchiole since the pores are now smaller. Thus air is trapped in the area furthest removed from the communications.

An explanation of the mechanism of air-trapping was offered [*2*]. During respiration the normal ventilated areas empty more readily than those that are collaterally ventilated. As any part of the lung empties, the passages narrow and the pores become smaller (there is good anatomical evidence for the alteration in the size of the pores with the degree of distension). Thus air enters areas that are collaterally ventilated more easily than it leaves them. (Fig. 10.) With slight degrees of air-trapping this means that there is a slight rise in pressure until equilibrium is reached. The more tortuous the path, the more efficient this "valvular" mechanism becomes; the pressure may rise until air entry with inspiration ceases and only occurs during forced expiration or even only with coughing. The equilibrium pressure clearly depends on the freedom of collateral ventilation.

Morphological evidence to support this was seen most clearly in the exudative phase of acute bronchiolitis. Passages beyond the obstructed bronchioles did not always appear dilated. Dilatation, occasionally even with disruption of alveolar walls, was obvious only when bronchiolar obstruction affected all bronchioles in a particular region. When slight change was found, it was seen in lobules some distance from normally ventilated areas, and affected the passages immediately beyond the obstruction. Since these affected passages lie towards the center of the lobule this lesion has been referred to as "acute focal (or centrolobular) emphysema" [*2*]. More severe acute lesions are found commonly in acute bronchiolitis affecting infants [*11*]. That disruption can occur at this stage is evident in those cases of extremely severe bronchiolitis in children (notably severe pertussis) in which rupture of alveolar walls is proved by the entry of air into the interstitial tissue of the lung.

The close association of obstruction and emphysema of the passages beyond the obstruction was readily demonstrable during the exudative phase of bronchiolitis. If the plug is expelled from the bronchiole (a likely event due to the pressure in the passages distal to it) air-trapping ceases. On the other hand, the bronchiole may become permanently obstructed and ultimately obliterated. (Fig. 11.) Wherever an obliterated bronchiole was found in an aerated region the passages distal to it were always emphysematous to some extent, but a clear topographical relation of obliterated bronchioles to emphysematous change in the air passages which the bronchioles originally supplied was, on occasion, only convincingly demonstrable, as in the localized lesions [*4*].

Persistence of bronchiolar obstruction, manifested by bronchiolar obliteration, prolongs the phase of air-trapping beyond the exudative phase of the bronchiolitis. The structural changes due to distention of the passages beyond the obstruction are clearly related not only to the distending force but also its duration of action. Moreover, with recurrent infections, and thus with progressive obliteration of more and more bronchioles, the changes can progress to the extremes associated with the clinical disease.

The distending pressure of trapped air has long been suspected as being a factor of cardinal importance in emphysema, a factor propounded by Laennec who first accurately described emphysema in 1819 [*12*]. Perhaps if Laennec had recognized the existence of collateral ventilation he would not have suggested the concept of the bronchiolar "ball-valve" or "check-valve" as the cause of air-trapping. It is remarkable that this concept should have held credence for so long. Head [*13,14*] has presented almost the only considered criticism of it, and he also indicated, in general terms, the possible significance of

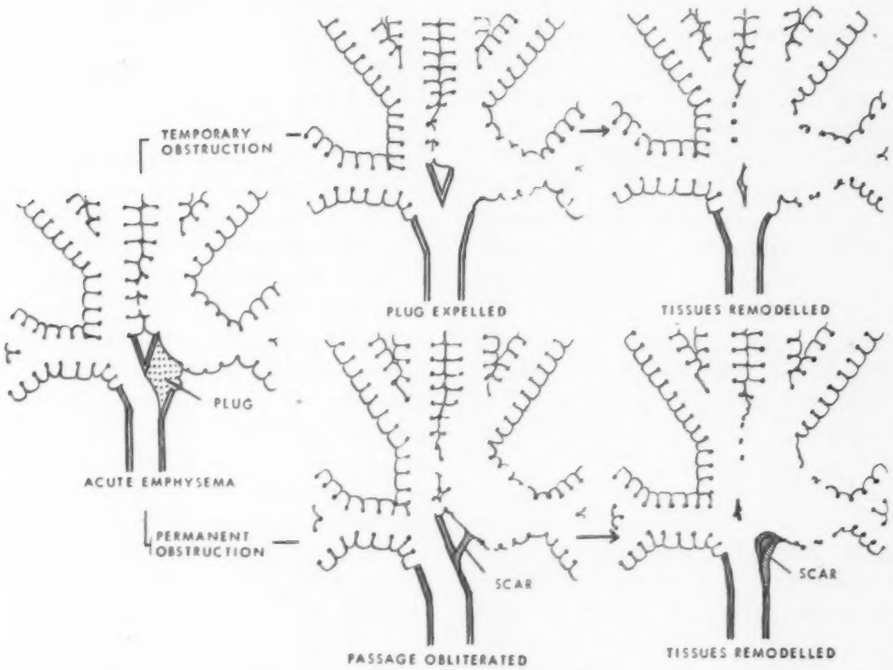


FIG. 11. A composite diagram showing the general problems involved in the hypothesis. On the left a sudden block of a first respiratory bronchiole by a plug is shown with dilatation and disruption of the respiratory bronchiole immediately distal to this; this is acute emphysema. The block may be temporary or permanent. Even if only temporary because the plug is expelled (upper series), some degree of permanent change may result in the form of permanent dilatation and some disruption of the walls. If the bronchiole becomes obliterated (lower series), trapping of the air persists until wide secondary communications are produced; coincidentally, the scar of the obliterated bronchiole becomes inconspicuous. Note (1) the development of a common pool in the area of developing emphysema and (2) the essential similarity of the end result with each process. In the late stages it is often impracticable to determine by which mechanism the emphysema developed.

trapping of collaterally ventilated air as a factor in the genesis of emphysema. Persistent ball-valve obstruction of air passages is only possible in the largest air passages such as the main bronchi; in smaller passages significant partial obstruction is an evanescent phenomenon—if the obstruction cannot be expelled the obstruction soon becomes complete due to accumulated secretions. Partial obstruction of small bronchioles by connective tissue (proposed by Spain and Kaufman [*15*] as the most significant pathogenetic factor) was uncommonly found in any but minimal forms, the remaining patent bronchioles in emphysematous lungs being more often dilated than narrowed. Moreover, as Head [*14*] pointed out, the most efficient "bronchiolar ball-valve" could not dilate normal air passages beyond the size that they assume in maximal inspiration, clearly an insufficient degree of dilatation to disrupt their walls.

Disruption. The essential lesion of emphysema is disruption of the walls of the alveoli opening into air passages and of the mesh of musculoelastic or elastic tissue outlining the passage. Disruption appears to begin by dilatation of alveolar pores and thinning of the alveolar walls.

The causes of this change are complex and have not been, by any means, completely elucidated. Two factors are involved: the disruptive force of trapped air and the loss of elasticity of the tissues. The nature of the disruptive force has been considered. This factor is of major importance and has been emphasized here. In circumstances in which air-trapping is severe the pressure gradient from the collaterally ventilated area to the adjacent area may be sufficiently great (during part of the respiratory cycle) to disrupt normal tissues. All morphological evidence has suggested that circumstances conducive to air-trapping had been present during the development of emphysematous lesions.

On the other hand, loss of elasticity is of considerable significance. When a stretching force is applied to a structure with impaired elasticity it will not return to its previous conformation. Repeated application of the force may eventually result in sufficient distention to produce rupture. The elasticity of the lung is not simply a function of the elastic tissue (a point emphasized previously [*3*]), but is contributed to by all the tissue components of the walls of air passages and alveoli and also by the surface tension of the film of fluid on its surface (and probably other factors besides). It is apparent, however, that impaired nutrition of the alveolar walls and the mesh around the orifices of the alveoli will impair elasticity and even lead to atrophy.

This focuses attention on the vascular changes. There are two possible means of producing ischemia of these structures. The first is the direct reduction of blood flow through the capillaries in the alveolar walls due to the constantly high pressure of trapped air in the area. The second is by occlusion or sclerosis of pulmonary and bronchial arterial branches more proximally. Cudkowicz and Armstrong [*16*] proposed that the essential factor in the genesis of emphysema was sclerosis of the bronchial vessels. Although a minor or secondary role may well be played by vascular factors, this proposition is not consistent with observations on the evolution not only of emphysema but also of vascular changes in other manifestations of chronic inflammatory disease of the lung [*6*]. There is no evidence that vascular changes *per se* are concerned with the pathogenesis of emphysema.

Elasticity may also be impaired as a result of direct inflammatory damage. This damage could occur during the exudative phase with subsequent reaeration of the damaged peripheral passages preceding expulsion of the bronchiolar plug. This sequence of events was inferred to occur commonly but, since in emphysematous lesions the original walls are either totally absent or represented only by unidentifiable residuums, this point could not be examined critically. Impaired elasticity has often been suggested as the sole factor in the pathogenesis of emphysema; these hypotheses are both incomplete and untenable. The most recent, and certainly the best reasoned hypothesis, is that of Heppleston [*17*] which purports to account for the focal emphysema of coal workers. Criticism of his proposition that the condition is solely due to the accumulation of coal dust in respiratory bronchioles has been offered [*2*]. The main objections are: (1) that the concept is inapplicable to similar (and more common) lesions containing little or no black pigment, (2) that it is assumed that the dilated passages are the original, although distorted respiratory bronchioles, and (3) that the part played by permanent inflammatory damage and obliteration of small bronchioles was not considered.

The consequence of disruption of alveolar walls and the mesh outlining passages are several. The most significant is that disruption increases the freedom of collateral ventilation of the affected area so that air-trapping is decreased. In the early lesions of emphysema in which only the passages immediately distal to the obstruction are affected and many of the more distal passages are normal, disruption is, in effect, compensatory so that considerable obliteration of small bronchioles may occur without notable loss of function [*3*]. In more advanced disease the remaining bronchioles open into what has been termed a "common pool" from which the more peripheral passages arise. Once the whole lobule is affected further disruption merely reduces the amount of functioning lung tissue.

Thus, where it is possible (as in large air cysts), measurement of pressures is of little value in elucidation of early phases since disruption tends to proceed until air-trapping is reduced, "equilibrium" being reached at a much lower pressure than that existing initially. Most lesions would be examined at this stage of equilibrium.

Disruption of the walls of air passages leads to the formation of secondary communications and, given sufficient time for the lesion to evolve, a more or less direct communication develops with adjacent regions supplied by patent bronchioles. Frequently the illusion that the emphysematous area was originally supplied by such bronchioles is created. Only in relatively slight lesions that have become arrested at an early stage of development could the true relations be demonstrated; since this also required the recognition of the obliterated bronchioles, such lesions were relatively uncommonly observed; several have been presented [*4*].

MORPHOLOGICAL TYPES OF EMPHYSEMA

Emphysema may be localized or generalized; intermediate forms were found and an arbitrary definition of generalized emphysema as emphy-

sema affecting all lung segments was proposed. Localized emphysema included both tiny isolated lesions as well as more extensive lesions, even those affecting all but one segment. The generalized disease frequently showed local accentuation of the emphysema, including superimposition of characteristically localized lesions such as apical bullae [*1*].

Study of the macroscopic and histological features of the condition showed that the evolution of the disease follows recognizable patterns which originally gave rise to and subsequently supported that hypothesis which has been proposed.

The earliest change in all forms of the disease has a characteristic conformation; dilated and disrupted air spaces were first seen in the earliest lesions affecting second and third order respiratory bronchioles (and sometimes also alveolar ducts) distal to passages showing evidence of inflammatory damage with actual or presumptive evidence of bronchiolar obliteration. Since these passages are all found towards the middle of the secondary lobule, early lesions were consequently centrolobular or focal, the periphery of the lobule being unaffected. Where there were indications of repeated incidents of bronchiolitis the changes were more pronounced. Exceptions to this were found in cases in which there was evidence that the lesion had developed as the result of a few (often only one) severe inflammatory incidents.

Purely localized lesions showed this typical focal change somewhat imperfectly, mainly since there were relatively great changes in adjacent structures and the septums outlining lobules were rarely identified. An emphysematous lobule surrounded by completely normal lobules was never observed; all strictly localized lesions showed evidence of considerable bronchiolar obliteration and alterations in architecture in the affected area [*4*]. Isolated ectatic bronchi or bronchioles were occasionally found in otherwise macroscopically normal lungs; most of the divisions of such passages were found to be obliterated. The peripheral passages once supplied by such obliterated bronchioles showed at least histological emphysema, but emphysema was pronounced only in those regions which were relatively remote from patent bronchioles. The most severe emphysematous change was seen in sites where collateral ventilation was restricted considerably by tissue impervious to air, such as pleura or scar tissue. Large bullae were usually subpleural, their base frequently being formed in part by scar.

The degree of emphysematous change in localized lesions is also determined by the impaired elasticity of the affected tissues. Damage of their structures during the original inflammatory episode (or episodes) may well play a part. The factor of altered elasticity is considered to be of particular significance in the formation of large subpleural air cysts.

Generalized emphysema showed similar features. This form of the disease is considered to be due to diffuse inflammatory damage to the small bronchioles and their immediate divisions. It was clear that the disease can develop over widely different periods of time. The most acute forms result from a single severe attack of acute bronchiolitis. In such circumstances damage is great and often many lobules become collapsed or consolidated, are not reaerated, and eventually become scars. Such lungs, therefore often, show much "diffuse fibrosis" [*18*]. Reports of autopsies on such patients have emphasized the most striking feature of each stage of the evolution of the condition rather than the natural history of the disease. Patients dying in the first few weeks are generally described as having "bronchiolitis obliterans" [*19,20*]; later arterial sclerosis may be the outstanding finding, as in the case described by Frothingham [*21*]. Only relatively few authors, such as Hyde, Hyde and Pokorny [*22*], have emphasized that these cases represent generalized emphysema of recent origin.

More commonly, generalized emphysema progresses slowly over years to the stage at which it is clinically recognizable as the result of the cumulative effects of minor inflammatory incidents. The evolution of such lesions was readily followed. The earliest changes mainly affected the distal orders of respiratory bronchioles so that a "common pool" formed in the middle of secondary lobules. Since collateral ventilation is relatively free between lobules in most cases, the condition advances uniformly, most lobules showing similar degrees both of bronchiolar damage and of emphysema. In general, with progress of the disease the whole lobule is eventually involved, a process which in most cases occurs over many years. The morphology of the focal lesion is, however, not constant. In some the focal pattern was soon lost as the process of disruption spread diffusely to involve the whole lobule at a relatively early stage of development of the emphysema, even

before the emphysema became macroscopically obvious. In others the focal lesion expanded and even compressed the unaffected periphery of the lobule, and with further evolution the focal lesions became macroscopically obvious.

In the second type, as opposed to the first, the walls of the much dilated spaces were frequently thick and often contained much black pigment. Part of this pigment was endogenous hemosiderin and part, particularly in coal miners, exogenous carbon-containing material [*2*]. The essential difference between the two lesions is considered to be due to the restriction of collateral ventilation due to the occlusion of alveolar pores by exudate and phagocytosed material. The much dilated spaces found in macroscopic focal emphysema cannot be assumed to be distorted original passages, as Heppleston [*17*] has suggested. Loss of elasticity of the walls by destruction of specialized tissues probably plays some part in the dilatation, but dilatation ceases when air-trapping is reduced by the formation of adequate secondary communications.

Further inflammation in both cases leads to diffuse generalized emphysema in which all lobules are affected. Disruption involves septums and, eventually, remaining bronchioles may open into huge common pools of segmental size or larger. At this stage of the disease collapse of bronchioles on expiration or coughing occurs in the emphysematous areas; this phenomenon [*3*] was demonstrated morphologically, confirming the observations of others using radiological and physiological technics. It considerably aggravates air-trapping in diseased areas and probably accelerates the progress of the disease.

ETIOLOGICAL FACTORS

From the morphological viewpoint the most significant etiological factors in emphysema are those related to inflammatory damage of bronchioles. The pattern and progress of the disease is largely determined by these factors. The site, nature and severity of inflammatory damage is determined on the one hand by the nature of the damaging agent, and on the other by the homeostatic mechanisms of the host.

Damaging Agents. These include: (1) Viral infections: These are of particular significance in the etiology of the generalized condition since they act diffusely, can produce severe damage in healthy active individuals, and are common and recurrent. Their importance in the genesis of respiratory tract infections is being increasingly recognized.

(2) Bacterial infections: The significance of pyogenic bacteria of the nasopharynx has been repeatedly stressed; bronchiolitis and bronchiolar damage by these agents occurs in every circumstance in which there is significant failure of the homeostatic mechanisms maintaining patency of the airways. Tuberculous infection is a common cause of localized emphysema. Diffuse bronchiolar damage and generalized emphysema occasionally follow widespread tuberculous infections [*23*].

(3) Chemical agents: Direct bronchiolar damage may result from the inhalation of toxic gases. Of slower action is that of inhaled dust containing silica, the dust being retained maximally in the region of the proximal orders of respiratory bronchioles [*2*].

Homeostatic Mechanisms of the Host. These factors are both general and specific. The general factors include "resistance" to infection. An analysis of the components of resistance to the invasion by growth and spread of organisms will not be attempted here.

Specific homeostatic mechanisms are those acting within the lungs, of which by far the most important are those concerned with patency of the airways. Failure of these mechanisms may be divided first into that due to overload either by excessive fluid in the bronchial tree (such as oversecretion of mucus due to asthma, inhalation or of irritative materials such as urban air or tobacco smoke) or by reduction of the lumen of the passages due to increased bronchial or bronchiolar tone (such as occurs in asthma or mild inflammation). On the other hand, failure of local homeostasis may be due to defects in the mechanisms themselves. Any lesion which interferes with the function of cilia, cough or collateral ventilation will result in increased inflammatory damage, particularly by secondary pyogenic bacterial infection of retained secretions. Local defects in these functions account largely for localized lesions in the lung, whether or not emphysema is present. Only a few of the agents, of which tuberculosis is possibly an example, ordinarily produce purely localized lesions in the absence of significant local failure of the mechanisms concerned with airway patency.

These concepts indicate the basis of the relation of chronic bronchitis to emphysema; this

relation has been discussed at length [*3*]. It was concluded that chronic bronchitis usually has two components. The first is due to chemical irritation of the mucus-secreting elements of the respiratory tract and of the musculature of the bronchial tree. This effect may precede the morphological development of emphysema and certainly accelerates its progress by prolonging the bacterial phase of respiratory tract infections. The other component is bacterial infection which is essentially bronchiolar rather than bronchial; persisting infection occurs at a stage of "cough failure" when secretions are retained for an abnormally long period. This is induced partly by overaction due to the chemical factors and partly by ineffective coughing due to the progress of emphysema. (The reduction of the maximal air velocity of coughing that occurs in emphysema is much influenced by the factor of bronchiolar collapse that occurs in advanced emphysema.) The stage of evolution of emphysema at which cough failure and persisting bacterial infection develop in a particular case clearly depends greatly on the importance of the chemical factor. The greater the chemical irritation, the earlier in the evolution of the disease cough failure occurs; in many cases "chronic bronchitis" becomes troublesome before the emphysema is clinically apparent. On the other hand, in the absence of factors inducing hypersecretion of mucus chronic bronchitis may not develop even in patients with advanced clinical emphysema.

SUMMARY

An outline of previous work on the pathological anatomy of emphysema and the natural history of pulmonary inflammation is presented, with the aim of producing a satisfying account of the pathogenesis of emphysema.

With a clear conception of the normal structure and function of the bronchial tree in mind, it is apparent that complete bronchiolar obstruction (especially by mucus) is a frequent, although usually shortlived phenomenon, even in health.

The close relation of bronchiolar obstruction to acute bronchiolitis is emphasized. In every respiratory tract infection, diffuse and relatively prolonged obstruction and inflammation of the smallest bronchioles occur. Such infections are not without sequelae; permanent damage is frequent and bronchiolar obliteration is not the rare phenomenon it has been considered in the past. It occurs (following obstruction and inflammation) in aerated as well as non-aerated lung tissue, aeration being maintained by collateral ventilation.

Although collateral ventilation is remarkably efficient, with sufficiently extensive obstruction of bronchioles air-trapping may result in the collaterally ventilated lung. This may distend and even disrupt passages immediately beyond the obstructed bronchioles (thus producing emphysema), particularly if the pressure of the trapped air is considerable, as with coughing.

Hence primarily, emphysema is seen to be the result of mechanical forces exerted by air trapped beyond obstructed bronchioles, the duration of the obstruction being one factor determining the degree of change. The significance of permanent inflammatory obliteration is obvious, the severity of the emphysema being, in part, proportional to the number of bronchioles obliterated. Along with the effect of air-trapping, in the exudative phase of bronchiolitis, alterations in the elasticity of the walls of the dilated passages add to the effect produced by the distending force.

These are the basic factors involved. The morphological and clinical variants of the disease are due to the interplay of numerous other factors which are considered in the section dealing with etiology. In this framework, the relation of chronic bronchitis to emphysema becomes apparent.

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Treatment of Tuberculosis Today*

A Five Year Report

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THIS is a summary of observations in over five hundred consecutive patients with proved tuberculosis admitted for treatment to the Central Washington Tuberculosis Hospital between June 1, 1952 and December 31, 1956.† Antituberculous drug therapy had not been given these patients before admission here; some had had previous collapse therapy or bedrest in other institutions. The cases include all types of tuberculosis—primary, reinfection, pulmonary and extrapulmonary—and all age groups. The diagnosis was proved either by positive cultures or positive pathological findings, or both. All patients had been given the three most effective and least toxic antituberculous drugs, streptomycin, para-aminosalicylic acid and isoniazid, along with early surgery when indicated. Streptomycin was given intramuscularly twice weekly, 1 gm. for adults and 0.5 gm. for children, para-aminosalicylic acid (P.A.S.) was given in doses of 10 gm. daily by mouth, reduced according to weight in children, and isoniazid 4 mg./kg body weight orally in three divided doses. No collapse therapy was given. The regimen included modified bedrest with full lavatory privileges for all patients, and they were permitted to go to the cafeteria as soon as they were physically able to after admission. Upon discharge all patients returned to their former occupations regardless of physical activity involved.

The patients were hospitalized for an average of 212 days. One hundred forty-two patients were treated surgically and 188 patients were treated medically. There was a minimum follow-up of over twenty-four months.

The 170 patients admitted for treatment from June 1, 1955 to December 31, 1956 are used for comparison to show (1) any change in incidence of resistant organisms at the onset of treatment, (2) how, with experience, the period of hospitalization has been reduced, (3) how this method of treatment has decreased the cost of treating tuberculosis, and (4) the number of chronic cases remaining.

METHODS OF EXAMINATION

Upon admission to the hospital all patients in whom sputum was not positive for tubercle bacilli on smear were further studied by culture of their gastric contents on three successive days, using modified Lowensteins' and Petragnani's media. The gastric contents were cultured every two months until discharge. The original culture was kept for comparison with subsequent cultures to determine whether bacterial resistance to streptomycin or isoniazid was present or if it developed. Roentgenograms of the chest were obtained on admission and at three-month intervals. Anteroposterior tomographs of both sides of the chest were taken at the end of three months. In tuberculosis of the bone all peripheral joints were opened, an adequate biopsy specimen of the lesion was taken, and some of the material removed was digested and cultured. (Because tuberculosis of the bone is so frequently associated with tuberculosis in other parts of the body, a diagnosis can often be established from these other sources). In renal tuberculosis retrograde pyelograms were obtained to determine the extent of envolvement and type of disease present.

RESULTS

Table I shows the vital statistics of the 188 patients in the medically treated group: sex, age groups, number of patients in each age group, deaths from tuberculosis and non-tuberculous causes. In Table II these medically treated cases are classified as to type of disease. The re-infection type is National Tuberculosis Association listed according to NTA standards. Indicated are the number of patients in each group, their average hospital stay in days, the duration of drug

† A report of the first year of this program was published in 1954 [*1*], two comparative reports appeared in 1955 [*2,3*], and other publications covering various phases of this program have appeared recently [*4–10*].

* From the Central Washington Tuberculosis Hospital, Selah, Washington.

therapy in days, average follow-up in months, and the number of reactivations.

Three and two-tenths per cent of the medically treated group and 2.1 per cent of the surgically treated group died of tuberculosis. It should be noted that 56 per cent of the total deaths from tuberculosis occurred in 7 per cent of the cases, namely, in children under six years of age who died of tuberculous meningitis. These children were all in general hospitals for an average of twenty days without specific therapy before the diagnosis of tuberculous meningitis was established. The life expectancy of a child with tuberculous meningitis before specific drug therapy became available was four to six weeks from the time he became sick enough to see a physician to the time of death. Thus the disease had almost run its course when these moribund children were started on specific therapy. Five of the eight children arrived at the hospital and died within three to five days after admission. It is generally accepted that if children with tuberculous meningitis can be kept alive for forty days on specific therapy they will live, but this is no guarantee that they will not be mentally deficient, as was one of the three who lived. This explains why, in Table II, these patients with meningitis received so little drug therapy and were hospitalized for such a short period of time. Those that live are kept in the hospital for a minimum of one year. The other tuberculosis death was a woman with far advanced disease in whom a thoracoplasty had been performed elsewhere seventeen years prior to admission here; a bronchopleural fistula and empyema developed, and she died suddenly thirty-nine days after admission.

TABLE I
MEDICAL VITAL STATISTICS
(101 Males, 87 Females)

Age (yr.)	No. Patients	Tuberculosis Deaths	Non-Tuberculous Deaths
0 to 6	17	5	0
6 to 18	29	0	0
18 to 35	43	0	0
35 to 65	73	1	5
65 and over	26	0	5

The cases of primary tuberculosis listed in Table II were in children six years of age or less, with definite x-ray changes and positive gastric cultures.

Table III lists the non-tuberculous deaths occurring during hospital stay and since discharge. Of the total of nineteen patients who died during hospitalization, autopsies were performed on sixteen, or 84 per cent. The cause of death in the patients who died after discharge was taken from their death certificates. It is interesting to note the high incidence of arteriosclerotic vascular disease and of carcinoma, particularly bronchogenic carcinoma. In the last category marked "Other," automobile accidents were responsible for four of the eight deaths after discharge. Of the 330 patients 3 per cent died of non-tuberculous disease during hospitalization

TABLE II
188 MEDICALLY TREATED CASES

Classification of Disease	No. Patients	Average Hospitalization (days)	Average Duration of Drug Therapy (days)			Average Follow-up (months)	Reactivations
			Streptomycin	Isoniazid	P.A.S.		
Tuberculosis, primary	16	229	218	205	38	24	0
Meningitis	8	148	162	160	0	22	0
Peritonitis and adenitis	2	43	182	182	43	18	0
Renal tuberculosis	4	144	214	214	144	33	1
Re-infection type (NTA classification):							
Minimal pulmonary	12	137	196	177	136	31	0
Moderately advanced	97	175	210	210	135	30	14
Far advanced	49	248	277	279	163	30	7

and they appear in the medically treated group because their associated disease (which finally caused their death) was of such nature that they could not be considered for surgical intervention. All these patients were in the age group of fifty-five years and over.

TABLE III
NON-TUBERCULOSIS DEATHS

Cause of Death	Hospital	Since Discharge
Cerebral vascular	3	1
Heart	2	3
Carcinoma	3	5
Other	2	8
Total	10	17

Early resectional surgery was performed for the following indications (provided that the candidates did not have complicating disease which would make resection impossible, such as recent coronary artery occlusion, pulmonary insufficiency, etc.): (1) positive cultures for tuberculosis after three months of combined drug therapy; (2) disease which would probably reactivate, such as bronchial stenosis, tuberculous bronchitis, bronchiectasis, caseous masses 2 cm. in size or larger, and cavitary disease; (3) reactivation following collapse therapy or combined drug therapy; (4) a previous history of irregular discharges, as in alcoholic patients; and (5) decortication after pleural effusion or previous pneumothorax to regain pulmonary function with resection of the diseased area of the lung.

Table IV shows the vital statistics of the 142 patients in the surgically treated group: sex, age group, number of patients in each age group, deaths from tuberculosis and from non-tuberculous causes. Two and one-tenth per cent of this group (three) died within ten days after surgery,

TABLE IV
SURGICAL VITAL STATISTICS
(84 Males, 58 Females)

Age (yr.)	No. Patients	Tuberculosis Deaths	Non-Tuberculous Deaths
0 to 6	5	0	0
6 to 18	6	0	0
18 to 35	49	1	0
35 to 65	82	2	0
65 and over	0	0	0

one each of coronary occlusion, pulmonary emboli and primary atypical pneumonia, therefore they are listed as tuberculosis deaths.

In Table v these surgically treated cases are classified according to type of disease. The reinfection type is listed according to NTA standards. Indicated are the number of patients in each group, their average hospital stay in days, the duration of drug therapy in days, average follow-up in months, and the number of reactivations.

The only reasons for selection in the groups treated medically and those treated surgically, other than those already stated, were first, the fourteen retired people who were treated medically because they were not good surgical risks

TABLE V
ONE HUNDRED FORTY-THREE SURGICALLY TREATED CASES

	No. Patients	Average Hospitalization (days)	Average Duration of Drug Therapy (days)			Average Follow-up (mo.)	Reactivations
			Streptomycin	Isoniazid	P.A.S.		
Tuberculosis of bone	17	237	219	189	130	35	0
Renal tuberculosis	6	156	247	272	159	33	0
Re-infection type (NTA pulmonary classification):							
Moderately advanced	55	220	300	293	165	29	1
Far advanced	65	262	310	306	166	27	3

(in five of whom reactivation occurred); and second, those patients who refused surgery during their first period of hospitalization (eight in this group). Other patients were not considered for resection for the following reasons: (1) the few who left against medical advice continued their drug therapy for the average period of time through the health department or through their private physician; others had severe hypertension but in one case resection was successfully carried out when reactivation occurred; some had such extensive tuberculosis that we believed resection was too risky to undertake during the first hospitalization (but resection was performed in two when reactivation occurred), one died of pulmonary embolus two days postoperatively.

TABLE VI
SUMMARY OF SURGICAL OPERATIONS

Operation	Total	Right	Left
Pulmonary:			
Pneumonectomies	18	2	16
Lobectomies	40	30	10
Lobectomies plus segmental	8	3	5
Segmentals	51	20	31
Decortications	3	1	2
Tailoring thoracoplasties at the time of resection	56	21	22
2–3 weeks after resection	..	2	11
Bronchopleural fistula	4	(Could not close 2)	(Closed 2)
Renal:			
Uretero-transplant	1	.....	1
Nephrectomies	3	1	2
Ureterostomy	2	1	1
Bone:			
Spine fusions	11	.....	.....
Knee fusions	3	2	1
Hip fusion	1	1	.....
Saucerization of fibula	1	1	.....

When we compare the patients with moderately advanced tuberculosis who received drugs only, with those who received drugs and were also treated by resection, the surgical group remained in the hospital forty-five days longer and received streptomycin and isoniazid about ninety days more and P.A.S. thirty days more; yet the reactivation rate in the surgical group was less than 2 per cent and in the medically treated group over 10 per cent. When we compare the patients with far advanced tuberculosis who received drugs only, with those who received drugs and were also treated by resection, the surgical group remained in the hospital only fourteen days longer and received streptomycin and isoniazid about thirty days more and P.A.S. two days more; yet the reactivation rate in the surgical group was less than 5 per cent and in the medically treated group over 12 per cent. Thus the patients in whom resection was performed have had fewer reactivations despite the fact that they were hospitalized only a few days longer than those in the medically treated group, and had only a few more days of drug therapy.

As Table VI indicates, the left lung was removed much more often than the right, the upper lobe of the right lung was the lobe most frequently removed, and the apicoposterior segment of the upper lobe of the left lung was the segment most frequently removed. One hundred twenty patients (36 per cent) were treated by resection. This percentage continued through 1955 and 1956.

The two bronchopleural fistulas which could not be closed were associated with tubercle bacilli resistant to both streptomycin and isoniazid. Those that could be closed were small bronchioles which could be sutured and the space obliterated by a small thoracoplasty. An effort was made to close these fistulas within four weeks after the original resection, before the development of empyema.

Our results in four of a total of ten cases of renal tuberculosis have not been satisfactory because of the marked stricture formation at the uretero-vesicular junction or uretero-pelvic junction, producing hydronephrosis. Two of the four patients had had nephrectomies because of tuberculosis several years before admission to this hospital; they had recurrence of symptoms and tubercle bacilli were recovered from the urine. Ureterostomies were performed to open the strictures at the uretero-vesicular junction because of the hydroureter and hydronephrosis of the remaining kidney. Urine cultures in one of these patients became negative; the patient died two years later of uremia and at autopsy the pathologist could find no evidence of tuberculosis. Cultures in the other patient have remained consistently positive in spite of continued drug therapy and organisms resistant to all antituberculous drugs are now present. Another patient had bilateral renal tuberculosis diagnosed in 1949. He was given streptomycin at another institution but dermatitis medicamentosa developed. In August, 1952, he was admitted to this hospital with bilateral pulmonary tuberculosis; intravenous pyelo-

grams disclosed that the right kidney was non-functional, there was a left hydronephrosis and hydroureter, the bladder was calcified and was smaller in size than a tennis ball. Some doses of dihydrostreptomycin were given along with isoniazid and P.A.S. and the left ureter was transplanted into the large bowel. He did well for four months, at which time his serum non-protein nitrogen began to increase; another intravenous pyelogram showed recurrence of hydronephrosis. Because of stricture formation at the site of anastomosis, the transplant had to be repeated. His nitrogen retention continued to increase until dihydrostreptomycin was stopped, and then it fell slowly. He was discharged and remained well for eighteen months, when he died of an intercurrent illness. At autopsy, the right kidney was completely destroyed, the anastomosis to the bowel was patent, and all the calcification had been absorbed from the bladder. The fourth patient responded well to drug therapy but had recurrence of symptoms one year after drug therapy were stopped. Pus was found in her urine but no tubercle bacilli were present. Drug therapy was resumed and continued for one year. Two years later retrograde pyelograms revealed no change in the contour of the renal pelvis but tubercle bacilli were recovered from the left kidney. When resected this kidney showed a cavitary lesion occupying the entire upper lobe.

Fusion seemed to be safe even in the presence of draining sinuses after an average of seventy-two days of chemotherapy. Those sinus tracts which had not closed by this time were secondarily infected with yeast-type invaders; however, when resected they healed by primary intention. There were fifteen successful fusions resulting from the first operation. The period of hospitalization for these patients was longer than for the others, averaging 237 days, because of the nursing care needed while still in a cast. There were no fatalities in the group and all have returned to their former occupations.

We have found that the culture of tissue from extrapulmonary tuberculosis is positive in a large percentage of patients despite chemotherapy. Consequently, we must conclude that therapy with the three drugs is less effective in retarding the advance of extrapulmonary lesions than in sterilizing pulmonary tuberculosis.

TOXIC REACTIONS

Para-aminosalicylic acid is the most expensive of the three drugs, the least effective and the most toxic. Twenty of the 330 patients had chills and fever within the first fifty days of drug therapy. This reaction may be severe and a small dose of the drug upon reinstitution of therapy will cause a recurrence within about two hours. Both the chills and fever, and the gastrointestinal complaints of pain or burning in the stomach, and diarrhea occur predominantly in patients with emphysema. For example, of the forty-eight patients with far advanced tuberculosis who were treated medically, three had typical allergic reactions and sixteen had gastrointestinal complaints severe enough to require discontinuance of the drug. Since the main purpose of P.A.S. administration is to delay the emergence of resistant tubercle bacilli, the toxicity of the drug defeats this purpose in more than one-third of the patients who need the drug most. The high incidence of peptic ulcer in patients with emphysema explains part of this difficulty [*16*].

Reactions to streptomycin are less common, a typical dermatitis medicamentosa developing in only five patients within the first fifty days of drug therapy. This reaction is characterized by a generalized rash, fever and an eosinophilia of over 10 per cent. When this develops administration of all drugs are stopped for ten days, then dihydrostreptomycin, 0.1 gm., is given, and if there is no reaction the dosage is increased 0.1 gm. daily until the patients are receiving 1 gm. of the drug twice a week. Patients who had a dermatitis medicamentosa reaction to streptomycin have a high incidence of "toxic nephritis" in response to dihydrostreptomycin, developing within a six-month period. It is characterized by the appearance of red and white blood cells in the urine, casts and an increase in the serum non-protein nitrogen. There is a high incidence of both reactions in renal tuberculosis. If a patient with a resectable pulmonary lesion has a dermatitis medicamentosa and is able to tolerate dihydrostreptomycin, resection should be carried out sooner than the three to four months after starting drug therapy recommended for other patients. Thus it is possible to give almost six months of drug therapy after resection before the "toxic nephritis" appears. Our patients are back at work, still receiving drugs, usually six weeks to two months after resection, as soon as we are assured that the postoperative gastric cultures for tubercle bacilli are negative. Streptomycin often causes dizziness for six hours after administration: when this is a problem the patients are given the drug after work when they can lie down.

While true allergy to isoniazid has been reported, we have not seen it in our first 500 cases, nor have we seen jaundice as a toxic manifestation. Two patients with a history of epilepsy had recurrence of convulsions but by increasing

anticonvulsant drugs it was possible to continue isoniazid for the necessary length of time.

No corticosteroids were used for any allergic reactions but cortisone has been given to our children with tuberculous meningitis during the first ten days of therapy when they had become subjectively worse with increase in temperature, nausea, vomiting and severe tension headache.

Penicillin is used as a "cover" drug for resection and in over 2 per cent of the patients an erythema nodosum type lesion develops.

TABLE VII
FOLLOW-UP OF LIVING DISCHARGED PATIENTS

Follow-Up	No.	Reactivations
X-ray plus gastric culture for tubercle bacilli	142	14
X-ray plus sputum smear and culture	8	4
X-ray plus clinic visit	94	9
X-ray sent to us	15	0
Report sent to us	13	1
No follow-up	25	0
Total	297	28

FOLLOW-UP OF DISCHARGED PATIENTS

The recent radical change in treatment coupled with the fact that all patients have returned to their former occupations, regardless of the physical activity required, immediately upon discharge made close follow-up imperative. In our previous experience, based on three gastric and sputum cultures made in this hospital in patients with x-ray changes characteristic of reinfection type tuberculosis and a positive Mantoux test, less than 6 per cent of patients with negative cultures have shown x-ray progression or have developed positive cultures within two years of their evaluation. This applied to patients before starting drug therapy but did not hold for those receiving drug therapy. Because of the validity of our criteria, based on our previous experience, an effort has been made to have our patients return to the hospital for gastric cultures a year after discharge and at least six months after discontinuation of drug therapy.

All ex-patients who have x-ray changes are admitted to the hospital for evaluation. If they have negative cultures for tubercle bacilli and the affected area clears quickly, they are discharged without further drug therapy. If the cultures are negative and they do not clear, a thoracotomy may be indicated to exclude the possibility of bronchogenic carcinoma.

As indicated in Table VII, we would not have discovered recurrence of active tuberculosis in fourteen of these patients in whom gastric cultures only were positive for tubercle bacilli had we depended upon sputum smear and culture, and x-ray change alone. Sometimes the gastric cultures may be positive for a year or more before the patient will admit to coughing up sputum or before there is roentgenographic evidence of new disease. Only six patients admitted to bringing up sputum and in two of these

TABLE VIII
DISCHARGE OCCUPATIONS OF PATIENTS

Occupation	No.	Reactivations	Total	Percentage (%)
Very light work	28	..	..	14.0
14 retired		5	..	....
14 pre-school children		0	5	....
Light work	125	..	..	4.8
83 housewives		5	..	....
31 students		1	..	....
8 office workers		0	..	....
3 sales personnel		0	6	....
Moderately heavy work	55	..	..	9.0
19 housework plus another job		2	..	....
19 foodhandlers		1	..	....
6 nurses and aides		0	..	....
5 engineers		0	..	....
4 cab and truck drivers		0	..	....
2 other		2	5	....
Heavy work	80	..	..	12.4
32 laborers		6	..	....
25 farmers		3	..	....
11 carpenters		0	..	....
5 mechanics		0	..	....
3 painters		0	..	....
4 other		1	10	....
Hard manual labor	9	..	..	11.0
5 loggers		1	..	....
3 steel workers		0	..	....
1 other		0	1	....
Total	297	27	27	....

NOTE: Eighteen women have had twenty-six pregnancies with no reactivations.

cultures were positive. The balance were seen in clinics by a member of this hospital staff, or x-rays were sent to us for review, or reports were sent from other clinics. All but twenty-five of the entire group (92 per cent) have been followed up for an average of more than two years since discharge. We assume that some of these are dead, and the remainder have not reactivated.

Table VIII gives a tabulation of the occupations to which the patients returned after discharge, together with the number and percentage of reactivations in each group. The occupations are classified according to caloric requirements, very light work requiring 1,500 to 2,000 calories per day, light work 2,000 to 2,500 calories per day, moderately heavy work 2,500 to 3,000 calories per day, heavy work from 3,000 to 3,500 calories per day and hard manual labor from 3,500 calories up per day. Many may take issue with placing housework in the "light work" category since the women carried on all their chores including washing, ironing and scrubbing floors, but when caloric requirements are taken into consideration few women need more than 2,500 calories a day.

REACTIVATIONS

Reactivation is here designated to mean the recovery of tubercle bacilli from those who had become negative both on smear and culture. Those who did very light work had the highest reactivation rate; this is readily explained since these were aged patients with extensive tuberculosis and serious associated disease which made resection impossible. The low reactivation rate of 4.8 per cent in the light work category is due to the fact that a large percentage of the group were women and they come to the hospital earlier in the course of their disease than do men. Of the twenty-seven reactivated cases, only eight were women, the remainder, nineteen, were men. When the twenty-six reactivated cases with pulmonary tuberculosis tabulated in this chart are divided into the medical and surgical groups, the latter group accounts for only four of the total, three doing heavy work (a laborer, a farmer and a plumber), and one doing moderately heavy work (a housewife with another job). Of the twenty-two patients in the medically treated group in whom reactivations occurred, five were on old age rolls, three were housewives, two were housewives with outside jobs, two were farmers, four were laborers, and there was one each of the following: logger, truck driver, surveyor, bartender, lumber mill worker and motel operator.

It was recognized that when drugs were used in courses they were less effective the second time they were given. Reactivation is an obvious indication that the drugs did not sterilize the lesion the first time they were used, therefore it is less likely that they would accomplish this on the second try. Because of this, all patients with reactivated disease were treated by resection if they were able to tolerate surgery. Those who had serious associated disease have since died so that with combined resection and autopsy material, we have been able to obtain tissue for pathological study from twenty-six of the twenty-eight patients with reactivated disease. Twenty-seven of the twenty-eight with reactivation returned to our hospital for treatment. (The last case, of renal tuberculosis, has already been discussed in detail.)

The more extensive the disease, the greater is the likelihood that serious pathological change is present. Thus minimal disease responds well to drugs only, and of those patients with moderately and far advanced disease, the surgically treated have fewer reactivations than the medically treated because the markedly involved tissue has been removed. In the past, women patients were advised against pregnancy for fear of reactivation; however eighteen of our women have had twenty-six pregnancies without reactivating. So we believe that it is the type of abnormal tissue that remains in the body which determines reactivation, and that physical exertion and pregnancy are not responsible.

When the pathological changes in those who were treated by resection during their first hospitalization are compared with the abnormalities found in patients resected after reactivation, a definite increase in the incidence of tuberculous bronchitis is noted, from 21 per cent to 72 per cent; caseous disease increased from 41 per cent to 78 per cent, and cavitary disease from 50 per cent to 67 per cent. The presence of a cavity has always been considered a serious handicap, both to conversion of cultures to negative and to the prevention of reactivation but apparently caseous disease and tuberculous bronchitis play an equally important role. Tuberculous bronchitis is easily demonstrated in the pathological sections but bronchial stenosis is seldom reported because the bronchus is commonly cut and sutured at the site of the stenosis. In the original 120 resec-

tions, bronchial stenosis was noted in the upper lobes in thirty-eight of forty-three cases, yet the pathologist reported stenosis in only four. Bronchial stenosis was found in nine of the eighteen patients in whom bronchoscopy was performed after reactivation, an incidence of 50 per cent. Thus there has been an increase of 15 per cent between the 120 who were resected during the first hospitalization and those with reactivated disease. It is important, therefore, to be able to see the segmental-bronchi in the upper lobes, and the only way that this is possible is with the use of right angle and fore-oblique telescopes.

BACTERIOLOGY

Eighty-four per cent of our patients had negative cultures for tubercle bacilli by the end of four months of drug therapy and in the first 330 cases all but two eventually converted to negative with combined drug therapy and resection; one of these two had such extensive pulmonary disease that resection was impossible and the other is the case of renal tuberculosis already described.

Complete resistance studies are available for 189 of the 330 patients discharged by June 1, 1955; the number and percentage of the group with organisms resistant to streptomycin and isoniazid are shown in Table IX. These sensitivity tests were made in three tubes of culture media, one containing 100 μg. of streptomycin per cc. of media, the second containing 20 μg. of isoniazid per cc. of media, the third a control tube. If the organisms grew as well in the streptomycin or isoniazid tube as they did in the control tube, the organisms were considered to be resistant. If there was no growth in either the streptomycin or isoniazid tube, the organisms were considered to be sensitive. If there was some growth, but not as much as in the control tube, the organisms were classified as partially resistant.

As is seen in Table IX, organisms inherently resistant to streptomycin and isoniazid were found even in patients who had never been given the drugs before; and since isoniazid was not available to us until June, 1952, these patients did not contract their disease from someone who had received the drug before. When these results are compared with the eighty-nine sensitivity studies made in 1956 on newly admitted patients, the percentage of resistant organisms is identical, so that we have not encountered an increase in the number of patients with resistant organisms. We attribute this to the fact that all known patients with tuberculosis are hospitalized and kept there until they are no longer contagious and have a very good probability of staying that way.

TABLE IX
RESULTS OF STUDIES IN 189 PATIENTS

Organism Sensitivity	On Admission		During Therapy	
	No.	%	No.	%
Streptomycin:				
Resistant	3	1.5	2	1.1
Partially so	2	1.1	2	1.1
Isoniazid:				
Resistant	20	11.0	4	2.2
Partially so	27	15.0	4	2.2

If a patient's cultures continue to be consistently positive, isoniazid-resistant organisms will appear after the first six months and streptomycin-resistant organisms between nine and eighteen months after starting drug therapy. Of our entire 500 cases, only three patients, admitted in 1953, are still in the hospital, one having been hospitalized continuously and the other two being patients with reactivated disease and consistently positive cultures. None of those admitted in 1954 are still in the hospital, three remain from 1955, and it is estimated that of the 109 admissions in 1956 only two will not convert their cultures to negative. These few chronic cases all have organisms resistant to both drugs. Variations in the sensitivity studies may occur, ranging from resistant to sensitive but this does not have the same significance as finding sensitive organisms at the onset of treatment and is probably due to a sampling process, i.e. the sensitive organisms come from one location in the lung and resistant organisms from another. These patients have a very poor prognosis and when resection has been attempted bronchopleural fistulas have developed in a high percentage; few converted to negative and stayed negative.

It has been our policy to digest part of the resected specimens for twenty-four hours in 2 per cent sodium hydroxide solution at 37°C., then centrifuge at 3,300 r.p.m. for twenty minutes. The supernatant fluid is poured off and a part of

the sediment is stained by Ziehl-Neilsen's method and is examined by microscopy. The remainder of the sediment is neutralized with hydrochloric acid and cultured in one tube each of Petragnani's and Lowenstein's media, then incubated for six weeks; if no growth is visible at this time it is called negative and discarded. An analysis of the results of smear and culture of the specimens is shown in Table x, correlated with the results of the last gastric culture made a few days before surgery. Those still positive before surgical intervention were almost all positive on smear and/or culture of the specimen. Of those with negative pre-surgical gastric culture, 8 per cent had positive smears and negative cultures, 18 per cent more had positive culture of the specimens and negative smears, and the balance, 74 per cent, had a negative smear and culture. Therefore, even though drugs may convert the gastric and sputum cultures to negative, this is no indication that the lesion necessarily is sterilized.

TABLE X
CULTURE OF RESECTED SPECIMENS

Pulmonary:	
17 still positive before surgery	
1 positive smear, negative culture	
11 positive cultures	
3 negative smear and culture	
2 not cultured	
100 with negative cultures before surgery	
8 positive smear, negative culture	
18 positive cultures of specimens	
74 negative smear and culture	
Renal:	
3 with negative urine before nephrectomy	
all positive by kidney culture	
Bone:	
4 specimens cultured	
3 positive	
1 negative	

In culturing extrapulmonary tuberculous tissues a much higher incidence of positive cultures is obtained. The resected specimens of lung from patients with reactivated disease also have a high incidence of positive cultures, for two-thirds of them will show growth, a much higher percentage than is seen when resection is performed during the first admission.

IRREGULAR DISCHARGES

Of the first 330 patients treated since this program was started in 1952, twenty-six (8 per cent) left against medical advice. When the group treated medically is compared with the group treated surgically, 10 per cent of the medical group left against medical advice and only 5 per cent of the surgical group, even though one of our patients in whom surgery was indicated has a history of previous irregular discharge from another institution. Our percentage of irregular discharges in 1955 and 1956 is less than this. If those patients who leave against medical advice still have positive smears or cultures, the Health Departments will issue orders of isolation and they are returned to us to be placed in a locked ward. We perform resection in these patients as soon as possible so that within six to eight weeks they can be discharged on out-patient drug therapy. The decrease in the average hospital stay may be responsible for the decrease in the number of irregular discharges, but I believe that two other factors are equally responsible: first, the patients know that they will soon be self-supporting again since they are sent back to their previous occupations immediately upon discharge regardless of physical activity; and second, and perhaps most important, an organized and definite plan of treatment is employed, and uncertainty of the patient is not increased by the uncertainty of the staff.

REHABILITATION AND OCCUPATIONAL THERAPY

The current concept of rehabilitation was formulated during the 1930's when the average age of the tuberculosis patient was around twenty years. For the most part these patients had no trade or profession and needed any education facilities that could be given them. Today the tuberculosis patients average over forty years of age and most of them have already learned and profited by a trade or profession. Those in this age group whose means of livelihood has been manual labor probably could not be taught a trade. A significant percentage of our patients come from the low economic level, many cannot read or write, and for these people rehabilitation to a lighter job is impossible for they simply do not have the mental ability to learn. If we order these patients to do no manual labor then they have no alternative but to receive public assistance for the rest of their lives. In our experience, patients who could be retrained spent at least a year being rehabilitated, then took jobs that paid less than their original positions, and before many months were back at their old jobs out of economic necessity.

Because of the continued shortening of the hospital stay, no effort has been made to carry on any occupational therapy. In spite of this our irregular discharges have decreased. The women had a homemaking course but because the period of hospitalization has been decreased so much it was impossible to maintain a large enough class to employ a teacher.

THE ECONOMIC ASPECTS OF THIS PROGRAM

In determining the cost of treatment of tuberculosis many factors must be considered. First is the actual cost of hospitalization, which is determined by multiplying the average cost per patient day by the average hospital stay; this figure can be computed from hospital records. The other factors are not so easily estimated but probably comprise a larger amount than the hospitalization costs. They include the cost of supporting the patient's family while he is in the hospital and afterwards while he is receiving rehabilitation training, and the cost of this rehabilitation itself.

The 312 patients treated in this hospital from January, 1950 to June, 1952, had an average hospital stay of 422 days and an average cost per day of $7.75. Thus it cost $3,270.50 just to hospitalize one patient, plus the cost of caring for his family during hospitalization and the entire family for one year after discharge. The 330 patients admitted between June 1, 1952, and discharged by June 1, 1955, were hospitalized 212 days and the average per diem cost was $9.43, a hospital cost of $1,999.16. Since all these patients returned to their former occupations upon discharge, their families were carried on welfare rolls only during the hospitalization period and there was no expense of rehabilitation. In 1955 the average hospital stay was 159 days and the cost per day was $10.92, a hospital cost of $1,736.28. In 1956 the average hospital stay was decreased to 139 days and the cost per day was $11.81, a hospital cost of $1,641.59. The increase in per diem cost is due to the decrease in hospital load, from an average of 115 patients between June 1, 1952 and June 1, 1955, to ninety-four for the year 1955, to eighty-four in 1956. It is not due to the cost of drugs since they cost less than fifteen cents per day per patient at the present time. The decrease in hospital load is not due to a decrease in the number of proved cases. We had more new admissions in 1956 than in 1951, with the same percentage of moderately and far advanced disease. Thus our incidence of tuberculosis is not decreasing. The decrease in hospital load is due to shortening of the period of hospitalization and to a decrease in the number of reactivated and chronic cases of tuberculosis. From the experience gained in this program, we find that those patients who require surgery can be resected at the end of three months of combined drug therapy instead of waiting four months or more and that they all do better if resection is performed before they have drugs for six months. This, of course, has been a factor in decreasing hospital stay.

COMMENTS

There are five characteristics of tuberculosis which make it a particularly difficult disease to treat; first is the tendency of tubercle bacilli to become resistant to any known antibiotic when they can continue to multiply in the presence of small concentrations of the drug; second is the tendency of blood vessels in the diseased area to become obliterated, which in turn further decreases the concentration of drugs where they are most needed; third is the tendency of the disease to produce destruction of tissue (caseation) which then has no blood supply and the drugs cannot diffuse into it in sufficient quantity to be bactericidal; fourth is the presence of viable tubercle bacilli inside macrophages so that an antibiotic such as streptomycin, which does not penetrate the cell membrane, is not effective; and fifth is the tendency to obstruct the normal drainage pathways, for example, in bronchial stenosis or ureterostenosis. Because of these difficulties a very careful evaluation of each patient is necessary if the tools we have today, in chemotherapy and resection, are to give the best results possible. It is impossible to predetermine from bronchoscopic and histologic examination which specimens will give positive cultures for tubercle bacilli. It is also impossible to distinguish between patients with negative gastric cultures and those with negative cultures of lesions resected after reactivation. It has been our policy to resect pulmonary lesions at the end of three to four months of combined therapy, before the emergence of drug-resistant organisms which increase the complications of resection. Whether or not resection is performed depends on the type of pathological change seen in routine anteroposterior tomographs taken after three months of combined chemotherapy, and, if there is a question of endobronchial disease, the results of

bronchoscopy using right angle and foreoblique telescopes. All bronchial stenosis and bronchiectasis should be resected. All large caseous foci over 2 cm. in diameter and all thick-walled cavities should be resected.

In reviewing our first 200 consecutive resections since 1951, we find that nearly all the bad results, i.e., bronchopleural fistulas, postoperative deaths from tuberculosis and reactivations, have occurred in patients who received drug therapy for more than six months before surgery. There are fifty patients in this group who received drugs longer than six months before surgery; only twenty-five have had a satisfactory result, ten died of progression of their disease and in fifteen bronchopleural fistulas developed. Of the 150 who received less than six months of drug therapy, there were two postoperative deaths, three bronchopleural fistulas (all of which were readily closed by resuture and a small thoracoplasty), none had positive sputum or cultures after resection, and so far in only two has reactivation occurred. If both sides need resection, the first procedure is carried out at the end of three months and the second is done six to eight weeks later; thus both are resected within the six month period. To judge from the results we have obtained, if a patient has a resectable lesion and does not have associated disease which contraindicates surgery, he should not receive long-term drug therapy because if reactivation occurs later the response to drugs will not be as good as with the first course, and the prognosis at surgery is poor.

All patients with active tuberculosis should be hospitalized to establish the diagnosis, the extent and type of disease, and whether or not resistant organisms are present. While certain groups of patients have a higher incidence of toxic reactions to the various drugs (for example, the P.A.S. reactions in patients with emphysema, streptomycin and dihydrostreptomycin reactions in patients with renal tuberculosis, and isoniazid reactions in patients with epilepsy) these reactions can and do occur in other patients, even in children. These reactions may be serious, and can be fatal if not recognized.

The purpose of the tuberculosis hospital is to isolate patients while contagious and to treat them so that there is reasonable assurance that they will not have reactivation of their disease. Since reactivation is related to the type of pathological change present, it is the physician's responsibility to rule out or remove, if possible, these types of reinfective tissue. As already indicated, the period of hospitalization has been materially shortened and the current program has decreased the cost of hospitalizing the patient with active tuberculosis by 50 per cent. The time spent in a hospital is not nearly as important as the treatment that is given during the hospital stay.

A great deal has been written about the drug treatment of non-hospitalized patients with tuberculosis [*17,18*]. It is worthwhile, therefore, to compare the results of this type of program with the results obtained from immediate hospitalization of over 500 consecutive patients and the use of controlled drug therapy, tomographs and bronchoscopy, with early resection when indicated. In the treatment program used in New York City a combination of two drugs was given. We have used all three drugs concurrently and continuously. The reports from the New York group indicate toxic reactions necessitating a change in drug combination in 4 per cent of patients treated. In our experience toxic reactions to isoniazid occurred in 1 per cent, to streptomycin in over 2 per cent and to P.A.S. in over 10 per cent. The New York group reports x-ray improvement in 50 per cent of their patients and 12 per cent show deterioration. The only worsening that we see occurs in patients with associated disease, of which bronchogenic carcinoma is the most common, being found in over 1 per cent. The few toxic drug reactions and the poor rate of clearing seen on x-ray in the New York experience can have but one explanation: all the patients do not take their drugs regularly.

At the end of twenty-four months of drug therapy the New York group reports that 83 per cent of minimal cases, 60 per cent of moderately advanced cases and 40 per cent of far advanced cases have a negative sputum culture. In our hospital all cases of minimal and moderately advanced pulmonary tuberculosis had negative gastric cultures and only 2 per cent of the far advanced cases remained in the "chronic" classification. Thus 48 per cent of their patients would be classified as "arrested" according to NTA standards, 12 per cent were "arrested with residual cavitation" and 40 per cent were still positive. Under our treatment regimen, 92 per cent of patients have negative gastric cultures and stable x-rays in an average period of hospitalization of 212 days, 3 per cent die of tuberculosis, 3 per cent die of associated disease

and 2 per cent remained in the category of chronic disease. These chronic cases would qualify as "arrested with cavitation" by New York's standards since they have reached the point where they deny bringing up sputum but have positive gastric cultures; after a few months the sputum returns and is positive first on culture and then on smear when resistant organisms appear. A large percentage of the New York cases designated as "arrested with residual cavitation" may be expected to reactivate [*11*] and when they do they will fall into the category of chronic tuberculosis with organisms resistant to the major drugs so they are no longer good candidates for resection. The New York group report that 45.4 per cent of their patients with positive sputum or cultures at the end of one year have isoniazid-resistant organisms. They also report that there has not been a marked increase in the percentage of isoniazid- and streptomycin-resistant organisms among their new cases [*12,13*], but this does not mean that the patients with resistant organisms are not contagious—it means only that a significant number of their contacts have not had time enough to develop reinfection-type tuberculosis.

If we had used only clinic visits for follow-up of our patients we would have missed more than half of those in whom reactivation occurred. These were picked up by gastric cultures when the patients returned to the hospital a year after discharge and six months after stopping drug therapy. The New York patients are not allowed to work so they and their families are dependent upon welfare for a minimum of two years for those whose cultures become negative for tubercle bacilli and the rest of their lives for the 40 per cent with persistently positive sputums or cultures. Our patients and their families receive welfare only for the 212 days of hospitalization since our patients return, immediately upon discharge, to their former occupations regardless of physical activity.

Thus drug therapy of non-hospitalized tuberculosis patients falls far short in every respect of what can be achieved with immediate hospital care. Outpatient treatment results in a relatively low percentage of conversion of sputum cultures to negative, and if the patients deny bringing up any sputum they are automatically considered negative, which is definitely not so. An alarmingly high percentage of consistently contagious cases will remain, as patients with chronic disease. Because of this great number of chronic cases such a program is not economical either in restoring patients to normal productive life or in saving tuberculosis funds. This type of program, in our opinion, may well lead to an increasing number of patients with resistant organisms as a result of contact with "open" cases.

Physicians have been lulled into a false sense of security by the fall in the tuberculosis death rate. They do not realize that the number of new cases each year and the extent of disease present in patients admitted for treatment are the same as they were five years ago.

CONCLUSIONS

1. An organized treatment program is described for all types of tuberculosis, using streptomycin, para-aminosalicylic acid and isoniazid, together with early surgery when indicated. This program has been in effect five years.

2. The three-drug combination resulted in negative sputum and gastric cultures in 84 per cent of all patients by the end of four months. In those whose cultures remained positive antibiotic-resistant organisms developed.

3. Resectional surgery is indicated in pulmonary tuberculosis for the following reasons: (a) to convert to negative the cultures of patients positive after three months of drug therapy, (b) to remove the types of infected tissues likely to cause reactivation of disease or which have already caused reactivation, namely caseous lesions 2 cm. or more in diameter, cavity and advanced bronchial disease including stenosis, bronchiectasis and tuberculous bronchitis, and (c) decortication for restoration of pulmonary function after extensive pleural change from pneumothorax or pleural effusion.

4. Tubercle bacilli resistant to a major drug (streptomycin or isoniazid) are found in patients on the first admission even though they have never received the drug and could not have contracted their disease from someone who had received the drug. The incidence of patients with resistant organisms on admission has not increased here over the five-year period reported.

5. In patients with persistently positive cultures for six months or longer organisms develop which are resistant to the major drugs and, when resected, have a high incidence of complications including bronchopleural fistulas, positive cultures after resection and reactivation after discharge.

6. Even though drug therapy may convert gastric and sputum cultures to negative, the

infected lesion is not necessarily sterilized because in a significant number of these patients a positive smear or culture is obtained from their resected specimens, or their disease is reactivated later.

7. Drug therapy is merely a tool in the treatment of tuberculosis, effective for a limited time and, if it is not properly used, the patient will have lost the opportunity for successful resection.

8. Reactivation is due to the presence of virulent, viable tubercle bacilli in certain types of infected tissue into which the drugs cannot penetrate. Therefore it is the physician's responsibility either to rule out the presence of such tissue or to remove it.

9. The extent of disease is a factor in reactivation because the more extensive the disease, the greater the likelihood of serious pathological change being present; thus minimal disease responds well to drugs only, whereas surgical patients do better than medical patients with moderately and far advanced disease because the source of reactivation has been removed.

10. With routine anteroposterior tomographs and right angle and foreoblique telescopes for use in bronchoscopy, it is possible to demonstrate most types of tissue involvement which are likely to cause reactivation.

11. Caseous disease is the most common pathological change found in patients in whom reactivation occurs; therefore, it is as dangerous a lesion as open cavitation when it has a bronchial connection which is manifest by positive cultures before drug therapy is started.

12. Endobronchial disease is the second most common pathological change found in patients in whom reactivation occurs. This applies both to tuberculous bronchitis and to bronchial stenosis of the segmental bronchi.

13. The purpose of follow-up is to detect reactivation of disease before there is progression. Therefore, gastric cultures should be obtained about six months after stopping combined drug therapy. Patients may have positive gastric cultures a year or more before there is x-ray evidence of new disease, or before they will admit to bringing up sputum.

14. While certain groups of patients have a higher incidence of toxic reactions to the various drugs (for example, the P.A.S. reactions in patients with emphysema, streptomycin and dihydrostreptomycin reactions in patients with renal tuberculosis, and isoniazid reactions in patients with epilepsy) these reactions can and do occur in other patients, even in children. These reactions may be serious and can be fatal if not recognized. All but the "toxic nephritis" from dihydrostreptomycin occur within the first fifty days of treatment.

15. The program herein described has reduced the mean period of hospitalization to 139 days for the 109 patients admitted in 1956. It has decreased the cost of hospitalization by 50 per cent. It has eliminated the need both for occupational therapy and rehabilitation since the patients are returned to their former occupations upon discharge regardless of the physical activity involved in their work.

16. Approximately 3 per cent of all patients admitted to the hospital died of tuberculosis, chiefly children of five years or less, with tuberculous meningitis. Another 3 per cent died during hospitalization of associated disease, mainly in the age group of fifty-five years and over. About 2 per cent remained chronic cases. Thus a satisfactory result was obtained in 92 per cent of all proved cases of tuberculosis.

17. Over the five-year period included in this report the number of new cases of tuberculosis found and the extent of the disease did not decrease.

18. This program has received excellent patient cooperation, as shown by the high rate of acceptance of the recommendation of resection (36 per cent of all admissions) and the few irregular discharges (8 per cent).

19. Drug treatment of non-hospitalized patients with tuberculosis falls far short in every respect of what can be achieved with immediate hospital care.

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Seminar on the Brain

Pathologic Physiology of Cerebral Dysfunction*

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THE clinical patterns resulting from interference with higher central nervous system function may be expressed as behavioral disorders, perceptual difficulties, intellectual impairment, abnormalities in motor or sensory spheres, or combinations thereof. These clinical disturbances have, for the sake of convenience, been classified into two arbitrarily identified groups—the organic and the functional brain disorders. The former are associated with demonstrable abnormalities of cerebral morphology, physiology or biochemistry. In the latter group no definite etiologic physical cause is evident; however, recent advances in neuropharmacology have intensified the belief that the so-called "functional" disturbances, practically all of which are psychiatric in nature, may nonetheless also be the result of metabolic derangements.

The clinical manifestations of central nervous system activity are expressed as the effects of a particular form of energy, the neuronal impulse. This energy, as well as that required by cerebral cells to maintain their structural integrity, is derived from oxidative reactions and is stored in the form of high-energy organic complexes, usually phosphates and perhaps sulfhydryl compounds. It should be obvious that interference with either substrate oxidation or utilization of the resulting energy (including that required for transmission of the neuronal impulse) may result in cerebral dysfunction or in impaired structural integrity of cerebral cells.

Numerous observations indicate that the brain is not a metabolically homogenous structure, and, as might be anticipated in view of their variable enzyme concentrations, different brain areas exhibit varying degrees of susceptibility to deleterious influences. Because of dependency upon an increasingly high rate of oxidative metabolism, liability to damage as a result of impairment of oxidative reactions appears frequently to progress along a scale of phylogenetic development, being most marked in the evolutionally newer and functionally more complex brain structures [*1*]. This is particularly evident when all parts of the brain are equally deprived of energy. On the other hand, various circumstances and agents may selectively interfere with energy production or utilization in certain cerebral areas without involving other brain regions [*2*].

The basic requirements for energy production and utilization by cerebral cells are: (1) substrate as a source of energy, (2) oxygen for the formation of carbon dioxide and water, (3) enzymes and coenzymes to catalyze the degradation of the substrate, and (4) proper mediation of interneuronal impulses. The manner in which the first three of these factors produce energy useful for neuronal activity is indicated by the familiar Embden-Meyerhof and Krebs cycles [*3*]. The various substrates, enzymes and cofactors known to be involved in the degradation of carbohydrate are presented in Table I. The fourth requirement is at present more speculative; it involves not only the axonal transmission of the neuronal impulse by progressive membrane depolarization, but also synaptic transmission by a variety of chemical mediators, the energy for the formation of which may also require oxidative reactions [*4*].

Table II presents findings on cerebral blood flow and metabolism in several conditions associated with disturbances in energy production.

Substrate Insufficiency. It is now well documented that the brain depends almost completely for its energy production upon the oxidation of glucose delivered by the circulating blood [*5,6*]. Hence, a sufficient reduction in

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TABLE 1
COMPONENTS IN CARBOHYDRATE DEGRADATION

Substrate	Enzyme	Cofactor
Glucose	Glucokinase	ATP, Mg^{++}
Glucose-6-phosphate	Phosphoglucoisomerase	None known
Fructose-6-phosphate	Phosphofructokinase	ATP, Mg^{++}
Fructose-1,6-diphosphate	Aldolase	None known
Glyceraldehyde-3-phosphate	Glyceraldehyde-3-phosphate dehydrogenase	DPN, HPO_4^-
1,3-diphosphoglycerate	Phosphoglycerate kinase	ADP, Mg^{++}
3-phosphoglycerate	Phosphoglycerate mutase	2,3-diphosphoglycerate
2-phosphoglycerate	Enolase	Mg^{++} or Mn^{++}
Phospho-enol-pyruvate	Pyruvic kinase	ADP, Mg^{++}, K^+
Pyruvate	Pyruvic acid oxidase	DPN, thiamine pyrophosphate, lipoic acid, coenzyme A
Oxalacetate + acetyl coenzyme A	Condensing enzyme	None known
Citrate	Aconitase	None known
Isocitrate Oxalosuccinate	Isocitric dehydrogenase	TPN, Mn^{++}
α-Ketoglutarate	α-Ketoglutaric oxidase	DPN, thiamine pyrophosphate, Mg^{++}, lipoic acid, coenzyme A
Succinate	Succinic dehydrogenase	Fe^{++}, flavin
Fumarate	Fumarase	None known
Malate	Malic dehydrogenase	DPN
	"Malic" enzyme	TPN

cerebral glucose delivery results in functional impairment and, if carbohydrate lack is of sufficient intensity and duration, permanent structural injury to cerebral cells will follow [*7*]. Reduction of cerebral blood flow alone is not a significant factor in depriving the brain of its glucose supply, chiefly because of the large excess of the substrate normally available in the blood. On the other hand, decreased blood glucose concentration sufficient to reduce cerebral glucose delivery below critical values is not an uncommon occurrence.

Oxygen Insufficiency. The brain is an almost completely aerobic organ. The partial degradation of glucose for the production of energy requires a large and constant supply of oxygen made available only by the circulating blood [*8,9*]. The oxygen consumption of the normal adult brain is approximately 50 cc. per minute (almost one-fifth of the total oxygen consumption of the entire body), and its delivery is accomplished by a blood flow of approximately 800 cc. per minute (about one-sixth of the total cardiac output) [*10*]. The oxygen in this amount of blood is greater than the cerebral metabolic requirements, and there is, therefore, usually a margin of safety in the event of a moderate degree of hypoxia or of reduction in rate of cerebral blood flow. This margin is protected by homeostatic mechanisms which tend to

become operative when its lower limits are approached. These regulatory mechanisms consist essentially of cerebral vasodilatation and increased systemic vascular resistance, which promote an increased cerebral blood flow. Nevertheless, corrective mechanisms cannot be expected to afford complete protection under extreme conditions, and there are, in fact, many clinical syndromes in which cerebral dysfunction results from impairment of cerebral oxygen delivery, due to severe reduction in available blood oxygen or to reduction in rate of cerebral blood flow. Generalized hypoxemia involving the brain is the consequence of low oxygen content of the arterial blood. This can result from inadequate partial pressure of atmospheric oxygen, obstruction of the respiratory tract, interference with pulmonary alveolar gas exchange, impaired pulmonary circulation, or inadequate availability of hemoglobin. Cerebral hypoxia may also result from local or generalized circulatory disturbances. Local disturbances causing brain damage may be classified as those due to obliterative vascular diseases of the brain such as cerebral atherosclerosis, thrombosis or embolism, and vascular compression by space-occupying intracranial lesions. The generalized circulatory disturbances causing cerebral hypoxia are those associated with acute hypotension, of which the most extreme example is cardiac arrest. Total interference with oxygen supply to the adult brain results in irreversible damage to the cortex in five to eight minutes [*11*].

Impairment of Enzyme Activity. The aerobic and anaerobic reactions involved in cerebral energy production require specific enzymes and coenzymes. Interference with cerebral enzyme activity may reduce or abolish cellular energy production. This interference may result from toxic inhibition or destruction of enzymes, or from lack of essential coenzymes necessary for the oxidation of glucose.

The metabolic heterogeneity of the brain undoubtedly depends upon qualitative or quantitative differences in enzyme complexes of the various cerebral structures. This may well explain the varying sensitivity of certain brain areas to different drugs and toxic substances as well as to deficiency of coenzyme factors and even to deficiency of oxygen and substrate.

Irreversible brain damage is not a frequent complication of primary enzyme inhibition, even though cerebral oxygen utilization may be depressed to, and maintained at, levels as low as those occurring with substrate insufficiency or oxygen lack [*12*]. This is probably because the metabolic requirements of cerebral cells may be significantly lowered as a result of enzyme insufficiency or because enzyme-regenerating structures retain their activity. As a result, the most practical method for protecting all parts of the brain against substrate or oxygen deficiency is to reduce requirements for these substances by inducing a general depression of cerebral enzymatic activity, for example by lowering the temperature of brain tissue [*13*].

TABLE II
DISTURBANCES OF CEREBRAL ENERGY PRODUCTION: TYPICAL VALUES*

	CBF	$CMRO_2$	CVR	MAP
Normal adults	55.0	3.5	1.7	90
Substrate insufficiency:				
Acute hypoglycemia	45.2	1.4	2.4	93
Cerebral hypoxia:				
Cerebral atherosclerosis	37.7	2.0	2.6	91
Acute hypotension (irreversible shock)	33.8	2.4	1.0	33
Cerebral enzyme inhibition:				
Hypothermia	21.6	1.3	4.1	92
Barbiturate intoxication	53.8	2.1	1.8	86
Acute alcohol intoxication	56.0	2.8	1.8	89
Hepatic coma	39.6	1.6	1.7	65
Uremic coma	50.0	2.2	2.3	107

* CBF = cerebral blood flow in cc./min./100 gm. of brain.
$CMRO_2$ = cerebral oxygen consumption in cc./min./100 gm. of brain.
CVR = cerebral vascular resistance in mm. Hg/cc. blood/min./100 gm. of brain.
MAP = mean arterial blood pressure in mm. Hg.

Many of the well known B-complex vitamins (Table 1) are constituents of coenzymes which are necessary for the production of energy from carbohydrate degradation [*14*]. For example, thiamine acts as a cocarboxylase in the decarboxylation of keto acids; riboflavin serves as a constituent of flavoadenosinediphosphate, and flavin mononucleotide governs oxidation reduction of fumaric and succinic acids; pantothenic acid is a necessary constituent of the ubiquitous coenzyme A; niacin, as a component of diphosphopyridine nucleotide and triphosphopyridine nucleotide, is active in controlling oxidation and reduction in several areas of the carbohydrate cycle; finally, pyridoxine, as pyridoxal phosphate, participates in deamination and transamination reactions for the formation of 5-hydroxytryptophan decarboxylase which is necessary for the biosynthesis of serotonin [*15,16*]. Nutritional deficiencies involving

these vitamins are not infrequently responsible for disturbances in central nervous system function.

Although lack of versatility may make cerebral metabolism relatively invulnerable to many noxious agents which affect other tissues dependent upon more numerous enzyme systems, the brain is extremely sensitive to some substances which may produce little change in organs with ambivalent metabolic pathways. Many drugs, such as the aliphatic depressants, bromides, heavy metals, alkaloids, etc., reversibly inhibit enzyme systems and impair cerebral function. Such agents may act by competitive inhibition of the enzyme or coenzyme, or by inactivating it through binding of its active radicals or by reversible denaturation of its protein moiety [*17*]. Endogenous depression of cerebral enzyme activity, such as occurs in uremic, hepatic or diabetic coma, is probably the result of such enzyme depression although the specific toxic substances have not as yet been conclusively identified.

An increase of the carbon dioxide tension of the blood delivered to the brain, which occurs in various clinical syndromes characterized by alveolar hypoventilation, may be associated with marked disturbances in cerebral function. The well known cerebral vasodilating effect of carbon dioxide is usually observed when an increase of arterial carbon dioxide tension of more than approximately 4 mm. Hg is achieved [*18*]. Nevertheless, the temporary remission of symptoms in catatonic subjects while inhaling 5 per cent carbon dioxide is most likely not due to augmentation of cerebral blood flow but to a direct cellular action. This statement may be justified by the usual adequacy of cerebral blood flow in uncomplicated schizophrenia [*19*].

The retention of carbon dioxide occurring in patients with alveolar hypoventilation may, on the other hand, produce a variety of mental manifestations, i.e., depression, anxiety, marked irritability, somnolence, confusion, delirium and coma [*20,21*]. As with most agents affecting the central nervous system, there are individual variations in susceptibility to carbon dioxide. Meduna has advocated the brief inhalation of 30 per cent carbon dioxide for the treatment of certain anxiety states [*22*]. The exact mechanism by which carbon dioxide stimulates or depresses the central nervous system is unknown although it has been suggested that the mesencephalic reticular formation may be particularly sensitive to changes in carbon dioxide tension [*23,24*]. There is the possibility that carbon dioxide may interfere locally with cerebral energy production by inhibiting those oxidative reactions of the Krebs cycle ultimately involving the liberation of carbon dioxide although no significant changes in the rate of total cerebral oxygen consumption have been observed during brief periods (ten minutes) of inhalation of 5 to 7 per cent carbon dioxide [*25*]. Other possibilities are that increased carbon dioxide tension may interfere with cerebral enzyme activity either directly or by virtue of changes in pH, or may produce uncoupling as will be subsequently briefly described.

It is interesting to note that marked *reduction* in carbon dioxide tension also produces changes in central nervous system function [*26*]. A characteristic symptomatology is observed, consisting of dizziness, impairment of concentration and memory, feelings of unreality, disturbances of consciousness, and acral and oral paresthesias. Hypocapnea due to hyperventilation is accompanied by reduction in cerebral blood flow [*27*]. Since more profound degrees of reduction can be accomplished by other methods without significant symptomatology [*28*], and a reduced carbon dioxide tension cannot interfere with oxidative reactions by mass action, it may be concluded that the manifestations of abnormally low carbon dioxide tension must be due either to a reduced pH (very unlikely), to interference with enzymes which are sensitive to changes in carbon dioxide tension, or to uncoupling. As already implied, one or the other of the latter two mechanisms is probably operative in hypercapnia.

Disorders of Energy Utilization. Situations are occasionally observed in which the energy derived from oxidative reactions is not quantitatively transferred to adenosinetriphosphate (ATP) for ultimate participation in neuronal impulse transmission. This phenomenon is known as uncoupling; the manner in which unused oxidative energy is dissipated is unknown. It is believed that this form of interference with proper energy utilization may be the mechanism of action of small doses of barbiturates, dinitrophenol, possibly phenothiazines, and in the hyperthyroid state. It is possible that this mechanism may be involved in other instances in which there are changes in cerebral function without demonstrable alteration of cerebral oxygen consumption.

As previously stated, the so-called "functional" disturbances of the central nervous system are those in which there is no demonstrable anatomical, biochemical or physiological abnormality. Nevertheless, the very nature of these disorders suggests that they may be the result of impaired integration of neuronal activity. In spite of the absence of conclusive evidence, it is quite possible that this lack of integration is related to abnormal neurohumoral transmission. Although neurohumoral mediating substances have been demonstrated to be synaptic transmitters in the peripheral nervous system, their presence and activity in the central nervous system has until recently been a matter of surmise by analogy. Even now, the problem has been greatly complicated by the probability that not only acetylcholine but other substances also may be centrally active. Acetylcholine itself (the distribution of which is most conveniently studied indirectly by means of demonstrating the presence of cholinesterase or cholineacetylase) has been definitely identified in various regions of the central nervous system [*29*]. The concentrations are highest in those portions of the central nervous system which are chiefly responsible for motor function. Relatively large amounts are found in the lateral filament and spinocerebellar tracts and the motor roots, with intermediate concentrations in the motor cortex. Nevertheless, additional brain areas must depend heavily for their function upon the presence of cholinergic fibers in view of the psychotomimetic properties of atropine and its derivatives. Recently Abood has described a new group of piperidyl benzylates, structurally related to atropine and possessing anticholinergic properties, which are very powerful psychotogens [*30*]. It has also been demonstrated that the intracarotid administration of acetylcholine in rabbits produces not only motor responses but also an awakening action which is duplicated by other cholinergic substances and is reduced by atropinization [*31*]. Both of these actions appear to be localized in the mesodiencephalic reticular formation.

It has long been recognized that certain catechol amines, i.e., epinephrine and nor-epinephrine, have a central excitatory action. Recently Vogt examined the distribution of nor-epinephrine in the dog's brain and found the highest concentration in the diencephalon (particularly the hypothalamus, mesencephalon and medulla oblongata, in that order) [*32*]. It is significant that its distribution was not related to the cellularity or vascularity of the brain areas, which makes it highly improbable that its existence in the central nervous system depends upon the presence of vasomotor nerve fibers. Studies by Elmadjian et al. of the excretion and metabolism of epinephrine and nor-epinephrine in man have suggested a differential pattern depending upon the emotional reaction of the subject [*33*]. Nor-epinephrine excretion appears to be related to the aggressive-active-hostile response, while epinephrine excretion seems related to the passive-anxious-fearful response.

According to Amin et al., serotonin (5-hydroxytryptamine) is also localized chiefly in subcortical regions in a distribution strikingly similar to that found by Vogt for nor-epinephrine [*34*]. Although there is ample evidence describing the peripheral activity of serotonin, its central function has not been clearly defined. Serotonin itself does not pass the blood brain barrier [*35*], and its presence in the central nervous system depends upon its formation from 5-hydroxytryptophan. The cerebral serotonin concentration can be increased in animals by the administration of large amounts of 5-hydroxytrytophan. In such circumstances central nervous system disturbances similar to those produced after the administration of d-lysergic acid diethylamide are noted (generalized somatic, autonomic and behavioral reactions). However, in man, nausea and intestinal disturbances produced by low doses of 5-hydroxy-tryptophan have prevented administration of amounts which might induce central effects.

It should be pointed out, however, that with the exception of acetylcholine there is little definitive evidence that nor-adrenalin, histamine or serotonin are, in fact, neurohumors. Before they can be accepted as such the following criteria (in addition to their presence in the central nervous system) must be satisfied:

(1) Specific blocking agents which prevent interneuronal transmission, e.g., like atropine for acetylcholine.

(2) Specific enzymes capable of hydrolyzing or oxidizing the neurohumor at sufficiently rapid rates so that no accumulation of the transmitter can occur, e.g., acetylcholine esterase.

(3) Following stimulation, electrical or otherwise, the quantity of neurohumor must increase, and specific biologic assay methods should be available for its quantitative or semiquantitative detection (acetylcholine on the eserinized

dorsal muscle of the leech; nor-epinephrine, the blood pressure of the pithed rat; serotonin on the pylorus of the rat's stomach).

The practical importance of these substances at the present time may be described on the basis of their sensitivity to the action of neuropharmacological agents. Many of these drugs have chemical structures strikingly similar to those of the putative central neurohumoral transmitters [*36*]. Although this similarity in structure suggests action by competitive inhibition, some of these drugs appear to cause or increase cerebral dysfunction while others tend to reverse spontaneous behavioral abnormalities.

It is interesting that reserpine releases from receptor sites both serotonin [*37*] and norepinephrine [*32*] and depletes their cerebral concentrations to approximately the same degree. It is uncertain, however, whether the clinical effect of reserpine (i.e., reduction of psychomotor activity) is due to either of these actions. On the other hand, administration of iproniazid, which (presumably in man also) increases cerebral serotonin [*38*] and norepinephrine [*39*] content, has clinical effects opposite to those of reserpine. The phenothiazine derivatives, chlorpromazine and promazine, etc., which are also effective in controlling increased psychomotor activity, have not been shown to affect the nor-epinephrine or serotonin concentrations in the brain stem although these compounds do have a peripheral ganglioplegic action [*40*].

It must be admitted that the experimental work is not entirely conclusive in terms of human physiology since these identifiable pharmacologic effects have been produced in animals by administering amounts of the drugs which are usually far in excess, proportionately, of those employed clinically in man.

As previously indicated, certain neuropharmacologic agents produce or intensify abnormal cerebral functional activity without demonstrable accompanying changes in the oxidative production of energy. It is only natural that the similarity of this situation to that of the spontaneously occurring psychoses should stimulate a search for structurally analogous endogenous compounds. The most logical candidate for this role is adrenochrome, a well known hallucinogen and an oxidation product of epinephrine. It has even been implied by the work of Hoffer [*41*] that d-lysergic acid diethylamide (LSD) may act by increasing the concentration of adrenochrome in the body. However, the unreliability of methods for quantitatively estimating adrenochrome renders such studies of dubious significance. This is particularly true in view of the fact that increased adrenochrome levels have not as yet been demonstrated in the endogenous psychoses.

Considerable attention has also been given to the search for a naturally occurring LSD-like substance since d-lysergic acid diethylamide produces an hallucinatory disturbance in some respects similar to schizophrenia. It is highly significant that LSD has been demonstrated to antagonize serotonin strongly [*42,43*], and it has been postulated that interference with normal cerebral serotonin activity may be the mechanism of action of LSD. Yet Cerletti and Rothlin [*44*] have found that bromination of lysergic acid completely nullifies all central effects except that of sedation, while not altering its antagonism to the bronchoconstrictor, vasoconstrictor and uterus-stimulating actions of serotonin. It therefore remains possible that the central inhibition of serotonin by LSD is of secondary importance. Nevertheless, it is proposed by Marrazzi [*45*] that serotonin is the natural cerebral neurohumoral synaptic inhibitor and that all the psychotomimetic drugs have a qualitatively similar action in depressing synaptic transmission in the central nervous system. The psychotherapeutic drugs, such as the phenothiazines, reserpine and azacyclonal, supposedly can prevent this inhibition in amounts that of themselves do not alter synaptic transmission.

It must be conceded that most of the evidence which has been presented has been derived from experiments confined to the subcortical regions of the brain. The present enthusiasm aroused by a reawakened appreciation of the importance of these centers in human behavior tends to obscure the role of the higher centers in the integration and synthesis of neuronal activity.

It may nevertheless be concluded from the foregoing observations that the so-called "functional" disturbances of the central nervous system will, in all probability, eventually be demonstrated to depend upon disturbances of energy utilization, the effect of which obviously cannot differ greatly from disturbances in energy production. It should not be surprising, therefore, that the clinical differentiation of organic and supposedly functional cerebral disturbances is often difficult and not infrequently impossible. We do not consider that

alterations in the state of consciousness are a satisfactory criterion in differentiating between the two groups of disorders, particularly in view of the fact that there is little agreement regarding the definition of consciousness.

Recent studies strongly suggest the possibility that psychological factors may be responsible for physiological changes, subtle but sufficient to cause well defined mental syndromes without revealing their true physiological components. The ordinary processes of thinking and feeling, of conation, attention, even of remembering, may well be closely bound to a physiological substratum, and the energy supplied for the functioning of complex associative processes must be derived from a physiological process. Unfortunately, however, the processes of dissociation have largely been interpreted in psychological terms and have thus been essentially removed from the biological sphere.

SUMMARY

Clinically, disorders of the central nervous system are expressed as dysfunction and are ordinarily classified as "organic" or "functional" syndromes. The former may be due to interference with the supply of carbohydrate or oxygen to the brain, to abnormalities of cerebral enzyme activity, or to disordered energy utilization or mediation of interneuronal impulses. Such disturbances, which are associated with or consist of anatomical, biochemical or physiological abnormalities, have not been demonstrated in the case of the "functional" disorders. Nevertheless, the nature of the "functional" syndromes suggests impaired integration of neuronal activity, which may be related to abnormal neurohumoral intersynaptic transmission.

The subject of chemical mediators in the central nervous system has only recently been studied intensively and is as yet but incompletely understood. It is probable, although by no means conclusively established, that most of the currently available neuropharmacologic agents—ataractics, "psychic energizers" and psychotomimetics—act upon or substitute for the neurohumoral mediators and thereby alter cerebral energy utilization. It is this latter factor which in the final analysis may be responsible for the outward manifestations of central nervous system activity, whether normal or organically or "functionally" abnormal. Hence, it should not be surprising that the etiology of disturbances in cerebral energy utilization may be difficult or impossible to identify as "organic" or "functional" on the basis of symptomatology alone. Indeed, it is the consensus that even normal mental activity is closely associated with an organic substrate; it seems an entirely reasonable corollary that the "functional" cerebral disorders are probably related to an organic, at least physiological disturbance, however obscure.

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Clinico-Pathological Conference

Polycythemia Vera, Compression Fractures and Hyperuricemia

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, a seventy year old white housewife, entered Barnes Hospital for the sixth time on February 5, 1957, with the complaint of severe back pain of four months' duration. She died on March 13, 1957.

The first admission to Barnes Hospital was from June 17, 1954 to July 8, 1954. In 1945, the patient had had bilateral thrombophlebitis. In 1949, the diagnosis of polycythemia vera had been made in another city. During the five years prior to this admission, she had received a total of 15 microcuries (mc.) of radioactive phosphorus, and several courses of treatment with triethylenemelamine were carried out. She had been on a meat free diet for four years. Phlebotomies had never been employed and the polycythemia had remained in good control. Six months prior to admission, thrombophlebitis of the left leg had developed, with tenderness in her leg for four to five days. Twenty days prior to admission, the patient fell, sustaining a fracture of the right femoral neck. After twenty days in traction she was transferred to Barnes Hospital.

The patient's past history was remarkable only in that she had undergone panhysterectomy and appendectomy for a cystic tumor of the uterus in 1940.

Pertinent physical findings included a blood pressure of 150/90 mm. Hg, tenderness over the left costal-vertebral angle, a palpable spleen tip, Buck's traction of the right leg, and palpable pulses in both lower extremities.

The red blood cell count was 6.89 million per cu. mm., the hemoglobin 16.9 gm. per 100 ml., the packed cell volume 48 per cent and the platelet count 435,000 per cu. mm. The white blood cell count was 9,050 per cu. mm. with 1 stab, 73 polymorphonuclear leukocytes, 8 lymphocytes and 18 monocytes. Examination of the urine showed no protein or sugar, and few white blood cells in the sediment. The fasting blood sugar on two determinations was 111 and 100 mg. per 100 ml. The non-protein nitrogen was 26 mg. per 100 ml. The cardiolipin reaction was negative.

On the fifth day, the right hip was nailed under general anesthesia and a bone graft was performed. Slight tenderness developed in the right calf without other signs of thrombophlebitis on the first postoperative day, and anticoagulation with dicoumarol was instituted. The patient was discharged without further complication. During her course, a persistent monocytosis, as high as 32 per cent was noted. At the time of discharge, the red blood cell count was 4.64 million per cu. mm. and the hemoglobin 13.4 gm. per cent.

The second admission to Barnes Hospital was from April 20, 1955 to May 2, 1955. Five months prior to admission, the patient's red blood cell count had risen to 8.0 million per cu. mm. and the hemoglobin to 18.5 gm. per cent. P-32, 2.8 mc., was administered, and the counts gradually returned to normal levels. Four months prior to admission the patient had noted numbness, discomfort and erythema of the right lower extremity, below the knee. Within ten days, the foot was cold and the diagnosis of occlusion of the superficial femoral artery was made. She walked on crutches, but cold sensitivity, erythema and weakness persisted, along with sharp pain and crepitation of the right knee. In the two weeks prior to her admission marked improvement occurred and the right dorsalis pedis pulsation became palpable.

The blood pressure was 200/110 mm. Hg.

The optic fundi showed grade 1 arteriosclerotic changes. The patient appeared plethoric. The heart was slightly enlarged to percussion and the second aortic sound was louder than the second pulmonic sound. A grade 1 apical systolic murmur was audible. The spleen was firm and palpable 6 cm. below the left costal margin. The liver was percussed 8 cm. below the right costal margin. There was crepitation of the right knee. A 2-plus bilateral pretibial and ankle edema was present. The right foot and calf appeared slightly erythematous and the erythema decreased with dependency. The skin appeared normal. Posterior tibial pulsations were absent bilaterally. The left dorsalis pedis pulsation was stronger than the right.

The hemoglobin was 17.5 gm./100 ml., the red blood cell count 7.17 million per cu. mm. and the white blood cell count 14,550 per cu. mm. with 1 eosinophil, 2 myelocytes, 3 stabs, 72 polymorphonuclear leukocytes, 4 lymphocytes and 18 monocytes. The urine specific gravity was 1.025, the protein negative and the urine sugar 1 plus. The non-protein nitrogen was 19 mg./100 ml., the fasting blood sugar 88 mg./100 ml., and the blood sugar taken two hours postprandially was 304 mg./100 ml. The serum cholesterol was 126 mg. per 100 ml. The total serum protein was 6.8 gm. per 100 ml. with the albumin/globulin ratio 5.0:1.8. The serum uric acid was 5.7 mg. per 100 ml. A roentgenogram of the chest demonstrated minimal left ventricular enlargement, elongation and calcification of the thoracic aorta, and calcified hilar and peritrachial lymph nodes. An electrocardiogram showed a Q wave in leads III and AVF.

One thousand ml. of blood was removed by phlebotomy, with the reduction in hemoglobin to 13.8 gm./100 ml. and in the red blood cell count to 5.25 million per cu. mm. P-32, 3.29 mc., was administered. Glycosuria disappeared following institution of a diet of 1,500 calories, and the blood sugar postprandially declined to 189 mg./100 ml. The blood pressure stabilized at 180/80 mm. Hg. Hydrocortisone was injected into the right knee and physiotherapy was begun. Five injections of histamine into the right femoral artery resulted in some apparent increase in the patient's exercise tolerance.

The third admission to Barnes Hospital was from September 20, 1955 to September 22, 1955. The patient's ability to walk without her cane improved, and claudication decreased in intensity and frequency, but dependent edema persisted in the left leg. The calves were occasionally tender.

The sole change in the physical examination was that the right foot was cooler than the left. Oscillometric measurements were unchanged, pulsations in the right lower extremity being diminished.

The hemoglobin was 15.3 gm./100 ml., the red blood cell count 6.56 million per cu. mm., the packed cell volume 49 per cent and the platelet count 171,000 per cu. mm. The white blood cell count was 33,500 per cu. mm. with 1 C-myelocyte, 2 metamyelocytes, 3 bands, 69 polymorphonuclear leukocytes, 1 lymphocyte, 23 monocytes and 1 young monocyte. The erythrocyte sedimentation rate was 1 mm. per hour. There was a trace of protein in the urine. The serum uric acid was 6.4 mg./100 ml. Roentgenogram of the right hip showed some sclerosis of bone along the fracture line and the bone density appeared increased in the femoral head with early cyst formation peripherally, suggesting aseptic necrosis.

Seven hundred fifty ml. of blood was removed by phlebotomy and the patient was discharged.

The fourth admission to Barnes Hospital was from March 2, 1956 to March 13, 1956. During the previous admission, the patient received a smallpox vaccination. One month later, generalized vaccinia developed which lasted four weeks, and for which hospitalization was necessary. In the five-month interval between admissions, she experienced increasingly constant dull pain in the right hip and buttock, unrelated to activity. X-rays one month prior to admission showed that the Smith-Petersen nail had moved its position by ¼ inch. Six weeks prior to admission severe pain in the left upper quadrant of the abdomen commenced and the patient received three x-ray treatments to the spleen, with shrinkage in its size. Diabetes was controlled with diet, and glycosuria was rare. Occasional dysuria was noted. Bilateral ankle edema, most marked on the left, persisted. The patient's weight had declined 10 pounds in five months.

The only change in the patient's physical condition was enlargement of the firm, notched spleen to 10 cm. below the left costal margin, and of the liver to 8 cm. below the right costal margin. There were a few 1 to 2 cm. erythematous areas at the site of the vaccinial eruption.

The red blood cell count was 7.59 million per cu. mm., the hemoglobin 15.2 gm./100 ml., the

platelet count 220,000 per cu. mm., the mean corpuscular hemoglobin 20 μμg., and the mean corpuscular hemoglobin concentration 33 per cent. The white blood cell count was 39,400 per cu. mm. with 7 C-myelocytes, 4 juveniles, 7 stabs, 63 polymorphonuclear leukocytes, 1 lymphocyte and 18 monocytes. The urine specific gravity was 1.022, reaction 5.5, protein 1 to 2 plus, and there was a trace of sugar. The urine contained innumerable white blood cells. The non-protein nitrogen was 33 mg. per cent. The cephalin-cholesterol flocculation test, thymol turbidity test, total serum bilirubin, serum alkaline phosphatase, and bromsulphthalein retention were all within normal limits. Roentgenogram of the right femoral head showed aseptic necrosis.

The Smith-Peterson nail was extracted under local anesthesia. P-32, 2.2 mc., was administered intravenously. The patient was walking prior to her discharge.

The fifth admission to Barnes Hospital was from October 11, 1956 to November 4, 1956. The pain in the patient's right hip improved markedly following extraction of the nail, but increased in severity in the three months prior to readmission. She was without pain when at rest, but experienced severe pain in the joint in the morning, until it "loosened." Episodes of dizziness had occurred four weeks and one week prior to admission. Ecchymoses appeared beneath the left eye one week prior to admission. She entered the hospital for evaluation of pain in the hip and for therapy to her now greatly enlarged spleen.

The blood pressure was 160/85 mm. Hg. There were ecchymoses below the left eye. The liver edge was 3 cm. below the right costal margin, and the spleen was 16 cm. below the left costal margin. There was 3 plus pitting edema of both legs. There was a ruddy hue to the right leg and trophic changes of the toenails of the right foot. There was no change in the oscillometric examination of the lower extremities.

The red blood cell count was 7.18 million per cu. mm., the hemoglobin 15.1 gm./100 ml., and the platelet count 502,000 per cu. mm. The white blood cell count was 73,000 with 1 basophil, 2 eosinophils, 6 C-myelocytes, 1 B-myelocyte, 6 bands, 53 polymorphonuclear leukocytes and 24 monocytes. The urine showed 1 plus protein and in the centrifuged sediment 0 to 2 white blood cells, rare red blood cells, and rare fine granular casts per high power field. The non-protein nitrogen was 21 mg. per cent. The blood sugar taken two hours postprandially was 99 mg./100 ml. The serum cholesterol was 118 mg./100 ml. and the uric acid 11.1 mg./100 ml. A first strength P.P.D. skin test was negative.

Radiotherapy was instituted, the patient receiving 1,700 roentgens in air to the left upper quadrant of the abdomen. The spleen shrank 5 cm. in size and became painful and tender. The white blood cell count declined to 11,650 per cu. mm., without significant change in the differential count. Three hundred ml. of blood was removed by phlebotomy. A sternal bone marrow aspiration showed a very cellular marrow. The differential count showed 1 eosinophil, 6 A-myelocytes, 1 B-myelocytes, 57 C-myelocytes, 12 metamyelocytes, 7 bands, 11 polymorphonuclear leukocytes, 3 lymphocytes and 2 monocytes. There were 20 normoblasts, 1 late erythroblast and 1 early erythroblast per 100 white blood cells. Megakaryocytes and erythroid elements appeared normal.

On the twelfth hospital day, severe lumbar back pain developed characterized by a steady dull ache with sharp lancinating pains laterally on any rotating movement of the trunk. No significant abnormalities were noted on physical examination. The non-protein nitrogen was 30 mg. and the serum uric acid 7.7 mg./100 ml. Films of the lumbar and dorsal spine demonstrated generalized osteoporosis, marked degenerative arthritis, and calcification of the abdominal aorta. The patient was placed on a bedboard, fitted with a corset, and heat was applied. Colchicine, without relief of pain, was administered until toxic symptoms occurred. Therapy with butazolidin,® methyltestosterone and diethylstilbestrol was instituted. At discharge, thirteen days after the onset of this pain, there was marked diminution in its intensity, but it was still present. At the time of discharge the serum uric acid was 6.6 mg./100 ml. and the urinary sediment showed many white blood cells, an occasional fine granular cast and many uric acid crystals. The patient was instructed to continue her hormonal therapy.

The sixth admission to Barnes Hospital was from February 5, 1957 to March 13, 1957. The patient's back pain persisted, but she was able to walk with a cane, and she left the city. Increasingly severe, spasmodic back pain developed. X-rays showed a compression fracture of the twelfth dorsal vertebra. A metal back brace and codeine afforded no relief and the patient became bedridden. She experienced tenderness

in both upper abdominal quadrants. Edema of the legs persisted at bedrest. The patient stopped taking the hormones. Her urine remained free of sugar. She lost 10 pounds in weight.

The blood pressure was 140/70 mm. Hg, the temperature 37°C., pulse 110 and regular, and respiration 18. The patient appeared as an elderly woman in severe pain and was apprehensive. There was evidence of dehydration. The patient cried whenever the abdomen or back were touched. There was tenderness along the entire spine, most marked over the spine from T10 to T12. A soft blowing systolic murmur was heard at the aortic and apical areas. The liver was enlarged to 7 cm. below the right costal margin, and the spleen tip was at the umbilicus. The bowel sounds were normal. The left leg appeared larger than the right; both were edematous.

The hemoglobin was 15.3 gm./100 ml., the red blood cell count 6.94 million per cu. mm., the platelet count 146,000 and the reticulocyte count 2.7 per cent. The white blood cell count was 40,950 per cu. mm. with 1 basophil, 1 eosinophil, 2 C-myelocytes, 6 metamyelocytes, 7 bands, 53 polymorphonuclear leukocytes and 28 monocytes. The urine specific gravity was 1.019, reaction 5.0, and there was a heavy trace of protein. Six to 8 white blood cells per high power field of centrifuged sediment and many uric acid crystals were seen. A culture of the urine was sterile. The non-protein nitrogen was 13 mg., fasting blood sugar 77 mg., serum calcium 9.9 mg., serum phosphate 4.0 mg., serum uric acid 5.1 mg./100 ml., and the serum alkaline phosphatase 3.1 Bodansky units. The serum albumin was 4.5 gm./100 ml. and the globulin 1.7 gm. The protein-bound iodine was 3.8 and 4.2 μg. per cent. The many roentgenograms obtained showed peritendinitis calcarea in the left shoulder, generalized demineralization of the bones of the entire skeleton, discoid atelectasis of the right lung, infiltration of the right lung and of the left lower lobe, compression fractures of D-11, D-12, L-1, and L-5, and atrophy of both kidneys.

The severe abdominal and back pain, at times generalized throughout the trunk and extremities, persisted. The patient was fitted with a new brace, and methyltestosterone, diethylstilbestrol, meprobamate, zoxazolamine and analgesics were commenced. Hydrocortisone was injected into the left shoulder at the point of maximum tenderness. Spikes in the temperature to 38.5°C. and 38.2°C. occurred on the second and ninth hospital days. Therapy with para-amino-salicylic acid, isonicotinic acid hydrazide, and butazolidin was begun. Thyroid, 30 mg. daily, was added to the regimen. All medications were discontinued when nausea and vomiting developed. An upper gastrointestinal series demonstrated splenomegaly. By the sixteenth hospital day, it was believed that the patient demonstrated some improvement and that her emotional status contributed to her disability. A lumbar puncture revealed normal pressures, a spinal fluid protein of 56 mg. per cent and serologic tests and colloidal gold curves were negative.

Dysuria was noted on the twentieth hospital day. Urinalyses showed 2 to 3 plus protein, many red and white cells and a trace of sugar. A few drops of gross blood was seen in the patient's urine on one occasion. A confluent growth of a paracolon bacillus, sensitive to tetracycline and chloramphenicol in high concentrations, was cultured from the urine. The non-protein nitrogen was 67 mg./100 ml., the serum uric acid 19.4 mg./100 ml., the serum sodium 134 mEq./l., serum potassium 3.9 mEq./l., serum CO_2 16.9 mEq./l., and serum chloride 105 mEq./l. An increased fluid intake was attempted and therapy with benemid® and colchicine was started. P-32, 1.8 mc., was administered.

On the twenty-sixth hospital day the hemoglobin was 12.9 gm., per cent, the platelets 451,000 and the white blood cell count 8,500 per cu. mm. with 28 per cent monocytes. By the thirty-first hospital day, the patient showed improvement and benemid and colchicine were discontinued. Chloramphenicol and tetracycline therapy was instituted. At this time, the non-protein nitrogen had risen to 80 mg. per cent and the serum uric acid had declined to 8.9 mg. per cent. On the thirty-third hospital day, nausea and vomiting developed and the patient became lethargic and then unresponsive. Parenteral alimentation was maintained. She became hypotensive, did not respond to pressor substances and died on the thirty-sixth hospital day.

CLINICAL DISCUSSION

DR. SOL SHERRY: Dr. Humphrey will demonstrate the roentgenograms.

DR. HARVEY A. HUMPHREY: The first film taken in June 1954 showed a fracture of the femoral neck. The bones were rather demineral-

ized, probably as a result of postmenopausal osteoporosis. In the ensuing films one may see evidence of the Smith-Peterson nailing procedure, and some ten months after the original fracture, avascular necrosis of the femoral head. After removal of the nail there was increasing density with flattening and deformity and subsequent development of arthritis. In the examination of the chest, concentric left ventricular hypertrophy with some dilatation was noted. Scars were present in each lower lobe, probably representing organized infarctions. A fairly pronounced degree of arteriosclerosis was evident in the thoracic and abdominal aorta. There was rather pronounced calcification of the tracheal and bronchial cartilages. A very large spleen was noted. Films taken in October 1956, showed pronounced arteriosclerosis, compression fractures of the L1 and D12 vertebrae, profound demineralization of the bones and some coarseness of the architecture. These were probably pathological fractures. A pronounced degree of splenomegaly with some displacement of the gas-filled stomach was seen. In February 1957, about a month prior to the patient's death, there was further splenic enlargement with more gastric displacement, and what appeared to be atrophic contracted kidneys. The films of the lower extremities showed phleboliths, medial type of calcification of arteries, and disuse atrophy of the bones of the extremity which had been fractures. A striking coarsening of the bony architecture was seen which I suspect may have indicated leukemic infiltration of the bones.

DR. SHERRY: We are beginning to recognize several different types of polycythemia: polycythemia vera; polycythemia associated with specific neoplasia; polycythemia secondary to chronic anoxia whether or not this be pulmonary disease, high altitude, congenital cardiac lesions or A-V fistulas; polycythemia associated with Cushing's syndrome; and finally, relative polycythemia, also referred to as neurogenic or stress polycythemia.

Our patient appeared to be a fairly good example of polycythemia vera since she fulfilled many of the characteristics described for polycythemia vera, and there was very little evidence to suggest any other etiologic mechanism. The usual patient with polycythemia vera will have the onset of symptoms of the disease in the fifty to sixty year age group; the red blood cell count will be above 7 million per cu. mm., the hematocrit over 60 per cent; thrombosis, hemorrhage, and the development of a hematological "myelopathy" (since P-32 therapy) are the major complications; and the average life span from the onset of symptoms is approximately thirteen years. Our patient had the onset of symptoms (bilateral thrombophlebitis) at age fifty-eight; she had red blood cell counts above 7 million per cu. mm., demonstrated thrombotic and hemorrhagic episodes, a hematologic "myelopathy," developed, and she died twelve years following the onset of symptoms.

However, there were two unusual features in her hematological picture: a persistent monocytosis and a lack of thrombocytosis. Dr. Brittingham would you comment on these?

DR. THOMAS BRITTINGHAM: The absence of thrombocytosis in polycythemia vera is not disturbing. In both our and Lawrence's experience, distinctly more than 10 per cent of untreated patients with polycythemia vera have normal platelet counts. Of course, by the time this patient was studied here she had received considerable treatment which would have depressed the platelet count.

With regards to monocytosis, the usual causes which come to mind are infections, such as tuberculosis and subacute bacterial endocarditis, Hodgkin's disease, and perhaps liver disease. Somewhat less well known, and perhaps a good deal more relevant to this patient, are the mild degrees of relative or absolute monocytosis which occur frequently in polycythemia vera, chronic myelocytic leukemia and myeloid metaplasia. Of the most recent thirty-three patients with polycythemia vera observed at this institution, mild monocytosis with absolute monocyte counts of more than one thousand were seen in fifteen. Occasional patients with myelocytic leukemia, polycythemia vera and myeloid metaplasia have very marked degrees of monocytosis. For example, our most recent patient with myelocytic leukemia had a white blood cell count of 159,000 per cu. mm. with 18 per cent monocytes, and the most recent patient to die with myelofibrosis had a white count of 36,000 per cu. mm. with 24 per cent monocytes. Last year, we observed a patient with polycythemia vera who had a leukocyte count of 54,000 per cu. mm. with 12 per cent monocytes. At postmortem examination, patients with extreme monocytosis associated with myeloproliferative disorders exhibit no differences from patients with the same diseases and normal monocyte counts.

DR. SHERRY: The protocol notes that at the age of fifty-eight thrombophlebitis developed in the patient and recurred several times during the course of her illness. On another occasion an arterial occlusion developed, and at other times she exhibited ecchymotic areas. Dr. Chaplin, would you comment on why patients with polycythemia are so prone to develop thrombotic and hemorrhagic complications?

DR. HUGH CHAPLIN: There are a number of reasons that are given for these complications. For one thing, these patients are in the age group when thrombotic phenomena are common and the underlying vascular conditions which predispose to thrombosis are present. Furthermore, the increased viscosity of the blood leads to sludging of the blood in the areas of poor circulation and presumably this leads to poor nutrition of the endothelium and the other layers of the vessel wall. These local factors plus the slow flow of blood may predispose to the formation of a thrombus. The increased numbers of platelets may also play a role However, as you have seen in this patient, thrombosis can occur without actual elevation of the platelet count. I think the hemorrhagic phenomena are also very interesting. There is an increased incidence of hemorrhage from specific sites such as the upper gastrointestinal tract, in part related to an increased frequency of peptic ulceration of the stomach and duodenum. The more general hemorrhagic phenomena in the skin, the eyes, intracranially and elsewhere are thought to be related to the increase in blood volume. This leads to vascular engorgement which is quite obvious from their appearance. Furthermore, there may be some damage to the vascular integrity as a result of the increased blood viscosity. Finally, clot retraction is impaired in these patients because of the mechanical interference of the large numbers of red cells in the blood. Lawrence [*1*] points out that a third of his patients who were followed up for a long period of time showed some lengthening of their prothrombin time. Furthermore, one series of patients with polycythemia has been described in whom the platelets showed deficient function. They are included in the group exhibiting "thromboasthenia" and this is often associated with hemorrhage. Very rarely fibrinogenopenia has been reported in polycythemia but this is certainly uncommon. However, there is good evidence that deficiencies in specific clotting factors are not required for an increased incidence of hemorrhage since the natives in the Peruvian Andes who have elevated hematocrits and red blood cell counts but normal platelets and normal clotting functions also have an increased incidence of hemorrhage.

DR. SHERRY: Dr. Harrington, what about the present status of erythropoietic factors as they may relate to polycythemia?

DR. WILLIAM HARRINGTON: This subject has been intensively studied in recent years, although the original observations were made in 1906. At that time two French investigators demonstrated erythropoietic stimulatory activity in the serum of rabbits rendered anemic by bleeding. The term "erythropoietin" was coined about ten years ago and is now generally applied to the serum factor or factors responsible.

The evidence for a humoral regulator of erythropoiesis may be summarized as follows: (1) Plasma or serum from either human subjects or laboratory animals with anemia of a variety of etiologies is capable of inducing an increased rate of erythropoiesis in recipient animals. (2) Serum from anoxic donors has a similar effect. (3) Parabiosis of animals, with subjection of one parabient to a low oxygen tension leads to accelerated erythropoiesis in both members. (4) Patients with patent ductus arteriosus with reversal of flow may have regional hypoxia, yet have an increase in erythropoietic activity in the normally oxygenated areas of their bodies.

The nature of erythropoietin is a subject of great controversy. There may be more than a single factor. One may be concerned with hemoglobin incorporation into red blood cells, and another with numbers of erythrocytes produced [*2*].

The site of elaboration of erythropoietin is unknown, although the fact that hypoxia limited to the lower half of the body in patients with a patent ductus and reversal of flow favors an intra-abdominal localization. Some have ascribed this role to the kidney but others have set forth evidence that the nephrectomized animal is capable of elaborating erythropoietin. As an indication of the present state of confusion it may be pointed out that serial extirpative procedures on every organ below the diaphragm

[1] LAWRENCE, J. H. Polycythemia. Modern Medical Monographs. New York, 1955. Grune and Stratton.

[2] LINMAN, J. W., BETHEL, F. H. and LAY, M. J. Studies on the nature of the plasma erythropoietic factors. *J. Lab. & Clin. Med.*, 51: 8–16, 1958.

have yielded negative results in the hands of at least some workers, while others have had the converse experience.

The chemical nature of the factor or factors is unknown although with the many excellent studies now underway, this information should be soon forthcoming. Evidence to date, however, has led only to the confusing suggestions that erythropoietin may be protein, mucoprotein, steroid, or lipid. The conflicting experimental findings may ultimately be reconciled by demonstration of the existence of more than one factor, and variations in test systems and species of animals employed.

Finally it should be pointed out that erythropoietic activity has been demonstrated in milk and urine. That erythropoietin in excess is responsible for the elevated red blood cell levels in polycythemia vera [*3*] is not uniformly accepted although the evidence is good and the concept attractive.

DR. SHERRY: During the patient's second admission to Barnes Hospital, there were "arthritic type" complaints referable to the right knee in addition to the symptoms of vascular insufficiency. A uric acid level was 5.7. Dr. Recant, do you think the arthritis could have been due to secondary gout, especially since higher uric acid levels were noted on subsequent admissions?

DR. LILLIAN RECANT: In the first place it is important for us to note that the correlation between the level of uric acid and the development of acute arthritic symptoms is a very poor one. This is particularly true in patients with secondary gout. Further, there is very little evidence that the uric acid level *per se* is etiologically significant in the development of the arthritic symptoms. In answer to your question, it is likely that the arthritis was a gouty symptom although it would be impossible to be certain.

DR. SHERRY: Would you comment on the metabolic differences between primary and secondary gout?

DR. RECANT: Secondary gout may be defined as the arthritic state associated with an elevated uric acid level which may occur in diseases other than primary gout. In these patients there may be one of two basic mechanisms operating in the production of the hyperuricemia. There may be either an enhanced and more rapid rate of formation of uric acid or a decreased excretion of uric acid. To deal with the latter briefly, patients with chronic nephritis may have significantly elevated levels of uric acid although occurrence of gouty symptoms is rarely observed. On the other hand, the use of drugs such as pyrazinamide, which produce hyperuricemia by inhibiting the excretion of uric acid, may result in the appearance of gouty attacks.

Those secondary gouty syndromes associated with increased urate formation are characterized by increased cellular turnover. The leukemias, the polycythemias and the hemolytic anemias are the major components of this group. Studies of uric acid metabolism in these patients have shown increased rates of uric acid formation, an increased size of the body pool of uric acid, and increased excretion of uric acid in the urine. In these patients, as opposed to the group with primary gout, a difference in the metabolic pathway for uric acid formation has been demonstrated. The source of the increased uric acid in primary gout is a rapid shunt mechanism from small molecules while in secondary gout, a slower pathway via nucleoprotein breakdown appears to be involved.

DR. SHERRY: Seven years after the diagnosis of polycythemia vera was made, it was noted that the patient's spleen was becoming progressively enlarged and tender; so much so that on two occasions the spleen was radiated. The white blood count progressively rose reaching a level of 73,000 per cu. mm. with many young forms in the peripheral smear and it was suspected that chronic myelocytic leukemia might have been developing in the patient. Dr. Loeb, would you comment on the development of "chronic myelopathies" in patients with polycythemia and what type of disorder do you believe this patient actually had?

DR. VIRGIL LOEB: It is important to point out that at our present state of knowledge, we are not justified in saying that the development of a "myelopathy," or whatever you wish to call it, characterized by a leukemoid peripheral blood picture and physical findings suggestive of leukemia, implies a fundamental change in this disease entity. We do not know whether it is a complication of the disease, whether it is part of the natural history of the disease, or whether it is a consequence of the radiation therapy which most of these patients receive. Data helping us in this regard are not available. There is no

[3] LINMAN, J. W. and BETHEL, F. H. The plasma erythropoietic-stimulating factor in man. *J. Lab. & Clin. Med.*, 49: 113–127, 1957.

question that a significant percentage of patients with polycythemia ultimately die with leukemia or myeloid metaplasia. If we group these together as one entity, most statistics will indicate that approximately 25 per cent of patients will die with evidence at autopsy of either leukemia or myeloid metaplasia. Reinhard [4] recently summarized the data on ninety-eight patients who were followed up at this institution since the advent of P-32 therapy, and found that nine of these patients died with acute leukemia, and twelve died with either chronic myelocytic leukemia or myeloid metaplasia. It is of interest that the incidence of acute leukemia was about 10 per cent, approximately the same as Lawrence's and Wasserman's statistics. In patients who have not received radiation, and there are very few on whom follow-up data are available, the incidence of acute leukemia is not high. However, it does occur, and Dameshek who treats his patients without radiation but with phlebotomy and a low iron diet, has recently reported two patients who died with acute leukemia. Therefore we cannot be sure whether the leukemia, which develops so commonly in these patients, is a consequence of therapy or is a part of the natural history of the disease. There has been a recent tendency to group diseases such as myeloid metaplasia, myelocytic leukemia, and polycythemia vera into a common category known as the myeloproliferative syndrome, and indicating proliferation of hematopoietic tissue in the bone marrow. If there is proliferation of the myeloid elements, the disease is called leukemia; if there is proliferation of the erythroid elements, it is called polycythemia vera; and if there is proliferation of the fibrous tissue elements, the disease is referred to as myelofibrosis with myeloid metaplasia. This concept is convenient, but there is very little biochemical confirmation for it. To be completely honest, we must admit that with our present knowledge we cannot differentiate myeloid metaplasia, or even myelocytic leukemia, from the late stages of polycythemia.

In retrospect, this particular patient received a great deal of radiation. She received approximately 25 mc. of radioactive phosphorus, 1700 roentgens of x-ray therapy, and many more roentgens from the numerous diagnostic films. It is possible that this amount of radiation may have contributed to her leukemoid blood picture. Careful review of the bone marrow slides which were obtained four months before death is not compatible with the diagnosis of leukemia. There was certainly proliferation of myeloid cells and monocytosis, but a morphologic diagnosis of leukemia cannot be made.

In summary, we must emphasize our ignorance concerning the development of myelocytic leukemia or myeloid metaplasia in polycythemia vera. Probably if patients were not treated with x-ray therapy, and yet could live as long as they do with such radiation, we might have the answer. Unfortunately, radiation therapy is still the best form of treatment, and the answer will not be available until the biochemist can differentiate leukemia from leukemoid reactions.

DR. RECANT: Is there not evidence that polycythemia with a leukemoid reaction can be distinguished from leukemia by measurement of the alkaline phosphatase or other enzymatic components of the white cells?

DR. HARRINGTON: In leukemoid reactions, including myelofibrosis as a late stage of polycythemia, the leukocytic alkaline phosphatase activity is increased whereas in chronic granulocytic leukemia it is decreased. Furthermore, the mean cell concentration of glycogen is low in granulocytic leukemia and elevated in leukomoid reactions, and there are other biochemical differences that have been studied. I think it is important to stress that we do not know the nature or identity of leukemia and accordingly should not discard the clinical diagnosis in favor of a biochemical diagnosis. I prefer to regard leukemia as a clinical and hematologic reflection of a number of possible biochemical lesions in the myriad of reactions required to produce a leukocyte. If this is correct, single criteria for diagnosis should be fallible.

DR. SHERRY: Renal failure was a prominent feature during the patient's last admission. Serum uric acid levels were as high as 19.4 mg./100 ml., and although the patient improved temporarily while receiving benemid, colchicine, and an increased fluid intake, she lapsed into coma and died. Dr. Bricker do you believe that postmortem examination will reveal an extensive gouty nephropathy?

DR. NEAL BRICKER: The differential diagnosis should take into account that the patient was elderly, that she had polycythemia, skeletal demineralization and hyperuricemia. I believe that the postmortem examination will reveal a

[4] REINHARD, E. H. and HAHNEMAN, B. The treatment of polycythemia vera. *J. Chronic Dis.*, 6: 332, 1957.

mixed lesion. The chronic lesion will include nephrosclerosis, and perhaps arterial occlusion with one or more areas of infarction. The former is supported on a statistical basis. The decrease in size of the right kidney in a patient with polycythemia is somewhat suggestive of arterial occlusion. With regard to the terminal acute event, I believe one of two explanations could support and satisfy the available data. The first is that the patient had acute pyelonephritis; the second that she had widespread deposition of urate crystals in the collecting ducts, and possibly in the renal pelves. The latter is a distinct possibility and perhaps both are present. Finally, three outside but unlikely possibilities should be mentioned. Since the patient was diabetic with proteinuria of long standing, it is conceivable she had Kimmelstiel-Wilson's disease. Secondly, she did have widespread demineralization suggesting the possibility of nephrocalcinosis. Finally, in view of the possibility of leukemia, there may have been leukemic infiltrates in the kidney.

TABLE I
CAUSES OF DEATH IN POLYCYTHEMIA VERA

Cause of Death	No P-32 Therapy* (% of 76 cases)	P-32 Therapy† (% of 73 cases)
Hemorrhage (cerebral, others)	30	12
Thrombosis (cerebral, coronary, etc.)	20	15
Renal disease (chronic pyelonephritis, etc.)	18	1
Leukemia	3	22
Other neoplasia	11	15
Heart failure or pneumonia	13	14
Miscellaneous	5	21

* VIDEBAEK, A. Polycythemia vera. *Acta med. Scandinav.*, 138: 179, 1950.

† LAWRENCE, J. H. Polycythemia. Modern Medical Monographs. New York, 1955. Grune and Stratton.

DR. SHERRY: At the time of death, the patient was considered as having polycythemia vera, diabetes mellitus, osteoporosis and pyelonephritis. In addition, chronic myelocytic leukemia was suspected. The terminal renal events were related to uric acid deposits in the kidney and pelvis. Although this diagnosis appears entirely reasonable, let us consider the possibility of some other unusual features which may be seen in patients with polycythemia.

Shown in Table I are the causes of death in polycythemia vera as noted in two large autopsy series; seventy-six cases studied by Videbaek [5] in Copenhagen, and seventy-three cases reported by Lawrence. Videbaek's group were not treated with P-32, whereas Lawrence's group included many patients who had received this therapy. It may be noted that the incidence of leukemia in the group treated with P-32 is considerably greater than in the group not treated with P-32. However it is also apparent that there is a very significant incidence of other neoplastic diseases in patients who die with a diagnosis of polycythemia vera. If polycythemia vera is a neoplastic disease, then the high incidence of other malignancies may represent the anticipated 10 per cent association of two neoplastic processes. However there is something peculiar in that certain neoplasms as shown in Table II, may occur more frequently in patients with polycythemia. As previously noted, this relationship may be real, since effective treatment of the neoplasm will cause a remission in the polycythemia. In the case of uterine myomas it has been suggested that large shunts may account for the polycythemia. Perhaps the same mechanism pertains for the cerebellar hemangiomas. Particular interest attaches to the group with hypernephroma since certain investigators claim that the kidney may be a major site of erythropoietin production. In addition to neoplasia, tuberculosis of the spleen may be associated with polycythemia. Schwartz and Fitzpatrick were able to collect thirty-five cases with this association.

TABLE II
NEOPLASMS AND INFECTIONS WHICH MAY BE CAUSALLY ASSOCIATED WITH POLYCYTHEMIA

Neoplasms:
Cerebellar hemangioblastoma (thirteen cases)
Large uterine myomas (five cases)
Multiple myeloma (four cases)
Hypernephroma (seventeen cases)
Infections:
Tuberculosis of spleen (thirty-five cases)

Since hypernephroma may present with an obscure clinical picture perhaps we should give further consideration to this possibility in our patient. In Table III are listed some of the unusual features of hypernephromas, as well as some

[5] VIDEBAEK, A. Polycythemia vera. *Acta med. Scandinav.*, 138: 179, 1950.

of the known characteristics of the association of polycythemia with hypernephroma. Dr. Bricker, in the light of this information, do you think it is possible that the patient also had an underlying hypernephroma?

DR. BRICKER: It is an interesting suggestion and there is nothing in the clinical course which rules it out.

DR. SHERRY: Dr. Chaplin, what do you think of the possibility of an underlying multiple myeloma?

DR. CHAPLIN: It is possible. First, let me point out several things. In Lawrence's four cases, only two of them would be accepted as multiple myeloma by most of us here. In two, the diagnosis was largely dependent on the finding of 10 to 14 per cent plasma cells in the bone marrow. This finding would not satisfy our criteria for a diagnosis of myeloma.

It is interesting that Bence Jones protein has been described in the urine of people with diseases other than multiple myeloma, and one of these other diseases is polycythemia. This finding is not frequent, but has been reported. Our patient had some proteinuria, but there is no mention of whether or not the urine was tested for Bence Jones protein. The serum globulin determinations were normal. Six of forty-five patients reported by Snapper had neither Bence Jones protein in the urine nor an absolute increase in their serum proteins. However, of the six patients who had neither of these diagnostic clues, electrophoresis of the plasma was abnormal in two or three. Although multiple myeloma is a possibility in our case, there is very little evidence to support it.

DR. SHERRY: Dr. Harford, do you believe that tuberculosis can be excluded?

DR. CARL HARFORD: It cannot be excluded. The tuberculin test was negative, but a negative response means little in an old lady with a debilitating disease. This patient would be expected to have a lowered resistance to infection if for no other reason than the large amount of radiation she received. It is interesting that when she was vaccinated, generalized vaccinia developed, also suggesting a lowered resistance to infection. Whether lowered resistance to viral infection would parallel resistance to tuberculous infection is, of course, a big question.

DR. SHERRY: I suppose all these suggestions are possible but there is little evidence to support any of them. Are there any other comments?

DR. LOEB: I would like to make one comment with reference to the comparison of Lawrence's statistics with those of Videbaek, in which the latter's data were derived from patients prior to the use of radioactive phosphorus. It is possibly misleading to emphasize the fact that Videbaek found only a 3 per cent incidence of leukemia in his patients, as opposed to 22 per cent or so in Lawrence's series. It should be noted that the average survival time was 6.7 years in Videbaek's series, as opposed to 13.3 years in Lawrence's series. Had the former patients been able to live for six or seven more years, there might have been a higher incidence of leukemia.

TABLE III
HYPERNEPHROMA AND POLYCYTHEMIA

1. Hypernephromas may present with an obscure clinical picture: Hematuria absent in 44 per cent (presenting syndrome: 3 per cent obscure fever; 3 per cent amyloidosis; 2 per cent debility as sole manifestation; 2 per cent polycythemia [30 × normal incidence]; 4 per cent misdiagnosed abdominal mass [spleen]; 9 per cent pulmonary, osseous and disease of the central nervous system).
2. Hypernephroma may exist for many years and then there may be late metastases.
3. When polycythemia and hypernephroma coexist, the polycythemia almost always precedes the diagnoses of hypernephroma.
4. Polycythemia disappears upon removal of renal tumor. Recurrence of polycythemia suggests metastases.
5. When polycythemia and hypernephroma coexist, usually splenomegaly, leukocytosis and thrombocytosis are absent. However, splenomegaly and leukocytosis have been described.

DR. SHERRY: Your point is well taken. We will conclude with a final diagnosis of polycythemia vera, myeloid metaplasia (perhaps chronic myelocytic leukemia), secondary gout with gouty nephropathy, pyelonephritis and severe osteoporosis. However, it would not be surprising if the pathologist were to find an underlying neoplastic disease, possibly a hypernephroma.

PATHOLOGIC DISCUSSION

DR. BARBARA ROSENBERG: Gross pathologic examination of this patient revealed pitting edema of both ankles and legs and a brawny induration of the right leg. The circumference of the right thigh and leg was 1 to 2 cm. greater than the left. Over the right hip was a curvilinear healed surgical incision and the right femoral head was deformed. The synovium of the right

knee joint was slightly roughened. The lumina of the right femoral artery and vein were completely obliterated.

When the chest was opened, the lungs appeared well aerated except for a few focal areas of atelectasis. There was a mucoid greenish material within the trachea and bronchi which corresponded in appearance to gastric contents; the mucosa was hyperemic. The heart was of normal weight and only slight atheromatosis of the coronary arteries was found. The thyroid was small, weighing 8.5 gm., and streaked with grey fibrous tissue throughout.

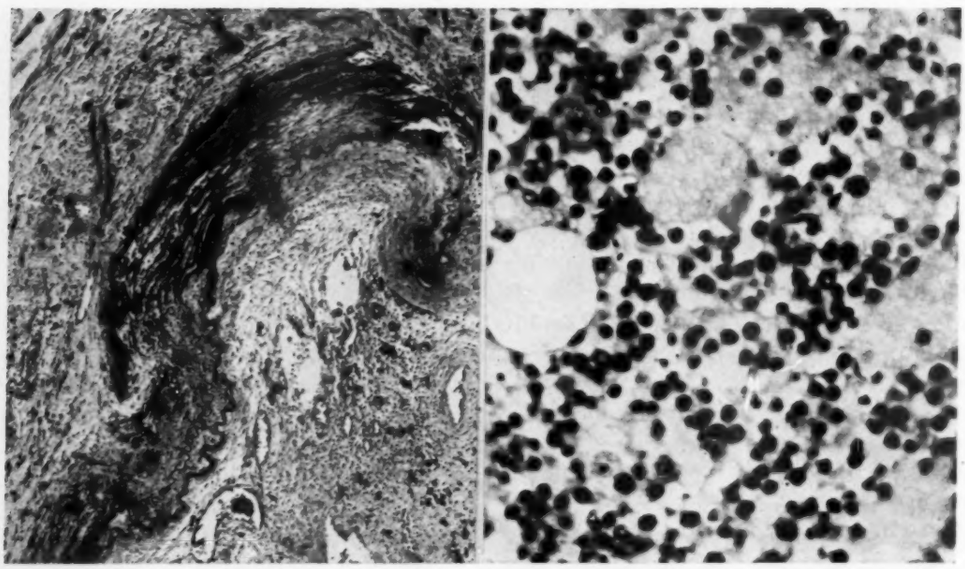
Upon opening the abdomen, approximately 200 cc. of a thin muddy yellow fluid was found in the dependent portions, particularly concentrated about the left upper quadrant, and in this area, there was a thick fibrinous exudate over the spleen and adherence of the omentum. There were no perforations throughout the gastrointestinal tract. The liver was slightly enlarged (2,160 gm.) but otherwise normal. The spleen was quite strikingly enlarged, extending 6 cm. below the left costal margin and weighing 1,365 gm. The capsule was thickened and covered by a fibrinous exudate. Bulging from the soft uncut surface were many yellow fluctuant nodules, some of which ruptured easily and from which drained a purulent exudate. On cut section, the spleen was found to be extremely soft and mushy and in most areas was a rather pale red color, while in some it was dotted with small abscesses or with larger triangular areas that resembled infected infarcts.

The kidneys were markedly enlarged, the right kidney weighing 200 gm. and the left kidney 310 gm. The surfaces were studded with small bulging abscesses, some of which appeared to extend into the capsule. Both kidneys were quite pale in color and on cut section these abscesses were again apparent in both cortex and medulla, almost totally destroying the normal architecture of the left kidney and slightly less numerous in the right kidney, the architecture of which was slightly better preserved. Several small decolorized triangular zones in the cortex of the left kidney were noted. In addition, in the right kidney, there were areas in the papillae which were gray and sharply demarcated, resembling papillary necrosis. To one of these necrotic papillae there was adherent a small crumbling yellowish stone. The pelvis of the left kidney was dilated, as was the ureter, and both were filled with pus. In the left ureter another stone was found impacted at the ureterovesicle junction. The adrenals were slightly enlarged, weighing 22.5 gm. together. The uterus and adnexa were absent.

Upon opening the cranial cavity, the superior sagittal sinus was found to be partially occluded by a recent mottled reddish brown thrombus. There were, however, no abnormal findings in the brain aside from a slight degree of atrophy. The bones throughout were soft and cut easily. The twelfth vertebrae was shortened. The marrow in all areas examined, including the femoral and tibial marrow, was a soft muddy brown. Cultures of the peritoneal fluid and of abscesses in the kidney and spleen grew a profuse growth of Proteus mirabilis and there was a slight growth of this same organism from postmortem culture of the heart's blood.

DR. ROBERT O'NEAL: The clinical and pathological diagnoses appear to agree very closely in this case but the severity of the pyelonephritis was all out of proportion to what might have been suspected clinically. The hypertension and diabetes in this patient, which morphologically might have proved rather interesting, had resulted in little pathologic change. There was no evidence of diabetes glomerulosclerosis and the pancreatic islets contained no hyaline; a special stain for beta cell granulation appeared perfectly normal. However, the pancreas did show a great deal of fatty replacement and fibrosis. Ateriolar walls were moderately hyalinized in the pancreas and slightly in the kidneys. This is considered to be associated with the hypertension and possibly the diabetes as well. But as evidence of diabetes and hypertension there was only this moderate hyaline arteriolar sclerosis and moderate pancreatic fibrosis with atrophy.

Numerous evidences of thrombosis were found. An atherosclerotic plaque in the aorta had ulcerated and a thrombus formed on it. This appeared to be a fairly recent thrombus, but a thrombus can remain unorganized in the aorta for a very long time. The femoral artery and vein on the right showed calcification of the media which is of the Mönckeberg type as Dr. Humphrey described radiologically, but the lumen of the femoral artery was occluded by a completely organized thrombus that had multiple recanalized channels. (Fig. 1.) This could have been an embolus from the mural thrombus of the aorta or could represent thrombosis *in situ*. The femoral vein also contained an old, organized recanalized thrombus. In addition, a



1 2

FIG. 1. The media of the right femoral artery is partially occupied by calcific material, appearing black. The wrinkled internal elastica is prominent and many irregular channels of recanalization are seen in the fibrous tissue filling the arterial lumen. Hematoxylin and eosin stain. Original magnification, × 75.

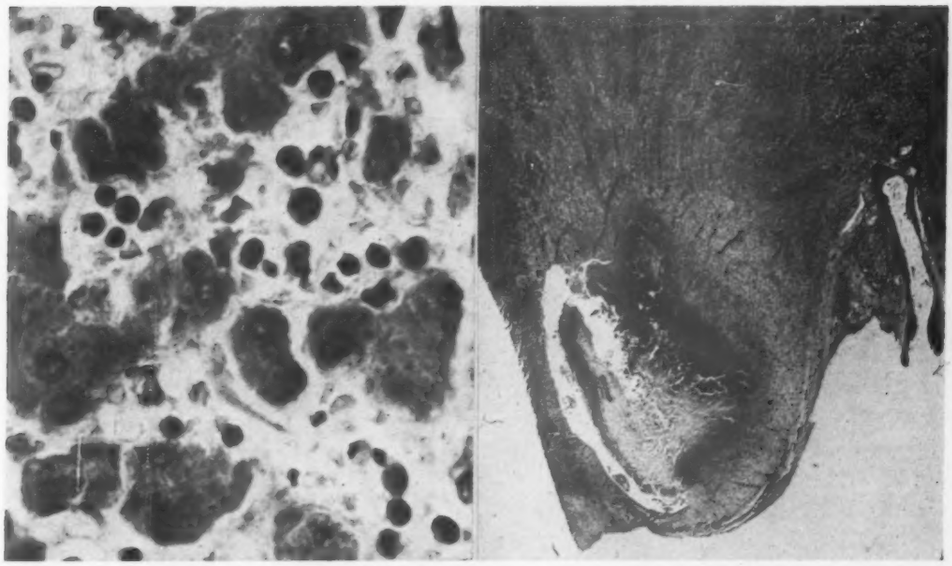
FIG. 2. The normally fatty femoral marrow is almost completely replaced by myelopoietic tissue. Near the single fat cell is a cluster of erythropoietic cells with small, dark nuclei. Hematoxylin and eosin stain. Original magnification, × 400.

recent thrombus that was not completely occlusive was found in the sagittal venous sinus of the brain.

Thrombosis of local vessels may have contributed to the development of aseptic necrosis following the nailing of the hip but we were unable to find any evidence of thrombosis in this area. There was a very good demarcation between an area of necrotic tissue and fibrous replacement of the marrow in the femoral head. The bony trabeculae in the area with fibrosis were distorted and widened and a large fibrous area repesented the tract of the Smith-Peterson nail.

Even in the femur the marrow was almost completely replaced by leukemic infiltration. (Fig. 2.) This was a characteristic myelocytic leukemia, although there were a few scattered cells that resembled monocytes. Throughout the marrow, small islands of erythropoiesis remained. In lymph nodes some megakaryocytes were found but the node architecture in general was well preserved, as we expect in myelocytic leukemia. Along the peripheral sinusoids there were early myeloid forms but in rather small numbers. A very mild infiltrate of leukemic cells was present in the myocardium. No foci of myelopoiesis were found in the liver but simply myeloid leukemic cells in the sinusoids, most of these recognizable as polymorphonuclear leukocytes. (Fig. 3.) Numerous magakaryocytes, as well as islands of erythropoiesis, were encountered in the spleen, but most of the infiltrated cells were myeloid. The splenic pulp was moderately fibrosed and, as usual, the increased weight of the spleen appeared out of proportion to the microscopic leukemic infiltrate.

The most spectacular pathological findings occurred in the kidney. Large abscesses in the cortex were continuous with the peritonitis that Dr. Rosenberg described. The lack of fibrosis indicated a recent origin. I believe that the abscesses of the kidneys, peritoneal cavity and spleen are part of the same process. Histologically, they were of similar age and appearance. In the papillae of the kidney there were large foci of the type that is so frequently seen in diabetic subjects with acute pyelonephritis; actually infarcts of the papillae of the kidneys. (Fig. 4.) In several areas of the kidney, somewhat removed from the abscesses, there were rather numerous leukemic cells and immature myeloid



3 4

FIG. 3. Hepatic sinusoids are dilated and contain numerous myeloid cells in various stages of maturation. Hematoxylin and eosin stain. Original magnification, × 690.

FIG. 4. An area of necrosis occupies almost this entire renal papilla. The central zone of necrosis does not contain leukocytes as did the cortical abscesses. Hematoxylin and eosin stain. Original magnification, × 3.

forms. Whether this was actually leukemic infiltration or a reaction of leukemic cells to the infection is impossible for me to say.

At autopsy, the patient's disease was chronic myelocytic leukemia with complicating infection and no evidence of polycythemia remained.

DR. SHERRY: Were you able to demonstrate uric acid calculi?

DR. O'NEAL: Not microscopically, but grossly. Dr. Rosenberg demonstrated these stones which we believe were one of the predisposing factors to pyelonephritis.

DR. SHERRY: I suppose that the only thing that prevented this woman from dying with a disseminated fungal infection was her limited antibiotic therapy.

DR. O'NEAL: I suppose so. We also thought a fungal infection likely in this situation and even got PAS stains on several sections of kidney but none were found.

Final Anatomical Diagnoses. Primary: Myelocytic leukemia with marked splenomegaly (1,365 gm.) and focal infiltration of dura, myocardium, perirenal fat and lymph nodes; history of polycythemia vera, nine years, treated with radioactive phosphorus and triethylenemelamine; osteoporosis, generalized, with compression fracture of the twelfth thoracic vertebrae and aseptic necrosis of head of right femur; organized thrombi in the right femoral artery and vein, with brawny induration of skin of right leg; edema of legs, bilateral; recent non-obstructive thrombus in the superior sagittal sinus; recent infarcts in the spleen and left kidney; obstruction of left ureteral orifice with urate stone; hydronephrosis and hydroureter, left, slight; pyelonephritis with abscess formation, involving entire left kidney, focal in right kidney (gm. + cocci demonstrated in tissue section; proteus cultured); papillary necrosis, right kidney; multiple abscesses of spleen; acute generalized peritonitis, with early fibrinous adhesions. *Accessory:* marked interstitial fibrosis, atrophy and fat replacement of the pancreas (history of mild diabetes mellitus); atrophy of the thyroid (8.5 gm.) (history of PBI of 3.8 and treatment with thyroid, 1 month); hypertrophy of the adrenals (22.5 gm.); arteriosclerosis of aorta, advanced; of coronary and cerebral arteries, slight; calcification in a hilar lymph node of the left lung; fibrous apical scar with pleural adhesions, left lung; arteriosclerosis of the pulmonary artery, moderate; accessory spleen; absence of adnexae, corpus uteri and appendix (history of hysterectomy, seventeen years).

Research Society Abstracts

Southern Society for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE TWELFTH ANNUAL MEETING, NEW ORLEANS, LOUISIANA, JANUARY 25, 1958

COMPARISON OF THE PHYSIOLOGICAL ALTERATIONS IN PNEUMONIA CAUSED BY PNEUMOCOCCI AND GRAM-NEGATIVE BACILLI. *James K. Alexander, Robert D. Leachman, Edwin M. Ory and Ellard M. Yow.** Dept. of Medicine, Baylor Univ. College of Medicine, Ben Taub Infectious Disease Laboratory and Cardiopulmonary Laboratory, Jefferson Davis Hospital, Houston, Texas.

Clinical and physiological observations have indicated distinct differences between patients with pneumococcal pneumonia and gram-negative bacillary pneumonias. This study was designed to correlate cardiopulmonary function with bacteriological, radiological and clinical findings in patients with pneumonia of differing etiology. Arterial blood studies were carried out in thirty-two patients, with observations on pulmonary ventilation, gas mixing, lung volumes and, in some instances, pulmonary vascular hemodynamics.

Patients with pneumococcal lobar pneumonia demonstrated mild hypoxemia and a tendency toward respiratory alkalosis. When radiographic and physical signs of pneumonia were present, respiratory alkalosis persisted, even after symptoms and fever had disappeared. Pulmonary blood flow was elevated, but pulmonary arterial blood pressures were normal. Residual volumes were slightly elevated, but seven minute nitrogen "wash out" values were normal. In contrast, patients with gram-negative bacillary pneumonias presented with severe hypoxemia, respiratory acidosis with extremely high arterial PCO_2 values in some instances. Residual volume was elevated, with defective intrapulmonary gas mixing and spirographic "air-trapping" in a single patient studied.

These findings suggest that the anoxia of pneumococcal pneumonia is due chiefly to failure to oxygenate blood perfusing exudate-filled alveoli, whereas in gram-negative bacillary pneumonia bronchiolar obstruction interfering with alveolar ventilation is the major physiological change.

* Throughout these abstracts asterisk designates member of the Southern Society for Clinical Research.

TEMPORAL LOBE SEIZURES AND BLOOD PRESSURE ALTERATIONS. *O. J. Andy, R. McC. Chinn, P. Bonn and M. Allen.* Jackson Dept. of Surgery, Division of Neurosurgery, Laboratory of Experimental Behavior, Univ. of Missississpi Medical Center, Jackson, Miss.

In a series of more than forty cats, blood pressure and electroencephalographic recordings were simultaneously made during seizures induced by electrically stimulating the amygdala and surrounding structures. Recordings were made on a Sanborn and Grass electroencephalograph, respectively. An electrical 30 cps., 1 m. second square wave was employed. Over 90 per cent of the experiments were made in the awake and unanesthetized animal.

In general, stimulation of the amygdala and immediately surrounding structures elicited a definite fall in blood pressure. The change ranged from 5 to 45 mm. Hg, in most instances occurring immediately after onset of the stimulation. The fall in blood pressure variously occurred during the (1) first few seconds of the seizure, (2) middle of the seizure, (3) its termination, (4) or following its termination. Occasionally a drop in blood pressure occurred at the onset of the discharge and returned to normal, with subsequent drop after its termination. The longer and apparently more extensive discharges were associated with the least degree of drop. This apparent paradox was explained by observations made on the hippocampal system after discharges which had a tendency to elevate the blood pressure. Blood pressure responses collectively graphed on twelve representative frontal sections through the amygdaloid and hippocampal regions revealed a greater tendency for blood pressure depression in the anterior central medial structures.

THERAPEUTIC EFFICACY OF INTRAVENOUS FAT EMULSION AND PROTEIN HYDROLYSATE AS DETERMINED BY NITROGEN BALANCE STUDIES. *Curtis P. Artz and Thomas K. Williams.* Jackson Dept. of Surgery, Univ. of Mississippi Medical Center, Jackson, Miss.

Recent advances in the preparation of fat for intravenous administration have yielded a stable 15 per cent cottonseed oil emulsion supplying 150 calories per 100 cc. Over 300 units have been given to more than thirty patients with a minimum number of minor reactions. An experimental evaluation of this preparation was carried out in patients and normal subjects by nitrogen balance study. Each patient served as his own control. The effects on nitrogen balance and weight changes were determined by using the following comparisons: (a) Starvation versus infusion of intravenous fat emulsion. (b) Starvation versus infusion of intravenous protein hydrolysate with fructose and alcohol (37.5 gm. protein and 800 calories/L.). (c) Intravenous fat emulsion versus intravenous protein hydrolysate solution. (d) Intravenous fat emulsion only versus a combination of fat emulsion and protein hydrolysate solution.

The results of these studies show that infusion of the fat emulsion had a definite protein-sparing effect. Patients with normal protein losses could be kept in positive nitrogen balance by means of total intravenous alimentation.

QUANTITATIVE MEASUREMENT OF PLATELET POTASSIUM, SODIUM AND WATER IN MYELOPROLIFERATIVE DISORDERS. *Joseph V. Auditore and Robert C. Hartmann.** Dept. of Medicine, Vanderbilt Univ. School of Medicine, Nashville, Tenn.

Previous studies in this laboratory demonstrated that in certain patients with thrombocytosis the serum potassium concentration may be falsely elevated, due to the disruption of the large number of platelets during coagulation. The present study was undertaken to determine whether the hyperkalemia was explicable solely on the basis of platelet mass or whether, in addition, there was an increase in the potassium content of platelets.

The potassium content of platelets isolated from normal subjects was found to be 69.1 mEq. of K^+ per kg. of platelets (wet weight) or 86.4 mEq. of K^+ per L. of platelet water. Platelet potassium was elevated in patients with polycythemia vera and myeloid metaplasia. The potassium content of platelets in patients with chronic myeloid leukemia was not remarkably different from that in the normal subjects. Platelets from both groups were found to have a water content of approximately 80 per cent and to contain small amounts [20 to 26 mEq. Na/kg. platelets (wet weight)] of sodium. In order to determine the normal physiological content of potassium, sodium and water in platelets a method was devised for the preparation of platelets free from red and white blood cells without the use of an anticoagulant. The method employs large amounts of blood (300 to 500 ml.) and is one of differential centrifugation.

EFFICACY OF REMOVAL OF PERITONEAL FLUID IN EXPERIMENTAL STRANGULATED INTESTINAL OBSTRUCTION. *William O. Barnett and James D. Hardy.** Jackson Dept. of Surgery, Univ. of Mississippi Medical Center, Jackson, Miss.

Stimulated by Burnett's demonstration of the beneficial result of irrigation of the peritoneal cavity in cases of suppurative peritonitis, an experiment was designed to determine the value of such irrigation in normal dogs receiving peritoneal fluid from animals dying of strangulated obstruction. Fifty-four dogs were used. Fluid obtained from the peritoneal cavity of animals dying of strangulation of a 15 cm. segment of ileum was injected into the peritoneal cavity of twenty-eight normal dogs to determine the lethal dose (3 cc./kg.). Ten other dogs received the same dose but the material was aspirated from the peritoneal cavity five minutes after injection. The survival time was not improved. In the third group of ten dogs receiving the same dose, the fluid was aspirated after five minutes and the peritoneal cavity irrigated with 1 L. of physiologic saline or Ringer's solution. The average survival time in this group was significantly improved, four animals recovering completely. Preliminary additional studies indicate that combined antibiotic therapy and peritoneal irrigation afford better protection than either alone.

FAILURE OF ACTH TO INFLUENCE ABSORPTION OF RADIOACTIVE SODIUM FROM THE PERITONEAL CAVITY AND FROM CHRONIC THIRY-VELLA LOOPS. *William O. Barnett, M. D. Turner and James D. Hardy.** Dept. of Surgery, Univ. of Mississippi Medical Center, Jackson, Miss.

In paralytic ileus the absorptive capacity of the intestine is often decreased. Moreover, adrenal cortical hyperactivity may significantly

limit the excretion of sodium from the body. Since stress of significant degree is usually associated with paralytic ileus, the effects of ACTH administration upon the absorption of Na^{24} from the peritoneal cavity and from chronic Thiry-Vella loops of ileum were investigated. Seventeen dogs were used. In the first group of animals (eleven) radioactive sodium was injected directly into the peritoneal cavity. Blood samples were collected at intervals before and after injection. An intravenous drip of 20 mg. of ACTH in 250 ml. of distilled water was started twenty minutes before the sodium was injected. Seven animals received no ACTH. There was no significant difference in the rate or degree of absorption of Na^{24} between the experimental and the control groups. The second group of animals (six) received Na^{24} directly into the chronic ileal Thiry-Vella loop. Four of these served as controls while two received ACTH as described. There was no significant difference in the blood levels of Na^{24} among the animals of this group. It was concluded that the absorption of Na^{24} from the peritoneal cavity and from ileal Thiry-Vella loops was not affected by adrenal cortical stimulation under the conditions of these experiments.

EFFECTS OF AFFEPENT CIRCULATORY ARREST UPON LIVER PH. *William O. Barnett, M. D. Turner and James W. Walker.* Dept. Surgery, Univ. of Mississippi Medical Center, Jackson, Miss.

The purpose of the experiment was to determine the effects of various degrees of afferent circulatory arrest upon the pH of the liver. Four groups of five dogs each were studied. Through an abdominal incision the tip of a Beckman quinhydrone glass electrode was inserted directly into the liver tissue and pH changes recorded. The animals in Group I served as controls. The hepatic circulation was not altered and the pH ranged from 7.01 to 7.22. In group II the portal vein was occluded for one hour. The liver pH was not significantly altered. In group III the hepatic artery was occluded for one hour following which the portal vein was occluded for an additional hour. Occlusion of the hepatic artery alone resulted in a mean depression of the pH to 6.79 after one hour. Portal vein occlusion for an additional hour was followed by an average pH of 6.30. In group IV the total afferent hepatic circulation was occluded for one hour and the mean pH of the liver was 6.43. The occluding clamps were removed and one hour later the pH had risen to 7.00. From the pH-time curves obtained, it was concluded that hydrogen ion activity correlated well with various degrees of hepatic circulatory impairment.

TRANSPORT OF DYES BY GOLDFISH RENAL TUBULES. *E. L. Becker* and S. Solomon.* Dept. of Medicine and Physiology, Medical College of Virginia, Richmond, Va.

A 16 mm. sound color film demonstrates the following phenomena associated with active transport of dyes by goldfish renal tubules. (1) Uptake of phenol red and chlorphenol red into the tubular lumen; (2) competitive inhibition of phenol red transport by bromcresol green; (3) self-blockade as shown by a reduced uptake of phenol red in the presence of high dye concentrations; (4) transport specificity as exemplified by the selective tubular accumulation of a red dye impurity found in trypan blue; (5) enhanced cellular uptake of neutral red in the presence of a high K-low Ca medium. Preparative methods are shown.

THE EVALUATION OF HEMODIALYZERS. *L. B. Berman and G. E. Schreiner.** Dept. of Medicine and Renal Laboratory, Georgetown Univ. Medical Center, Washington, D. C.

The problems involved in evaluating the total performance and efficiency of a hemodialyzer, and in comparing various types of apparatus, include differences in patient size, blood flow, pre-dialysis blood levels, surface areas of cellophane, and the method of cellophane washing. The continuous development of new kinds of hemodialyzers intensifies the need for an objective method of evaluation and comparison.

In a series of twenty clinical dialyses, using both the rotating drum and twin-coil dialyzers, we have measured flow rates of blood through the machine by indicator dilution technics. Simultaneous entrance, exit, and bath samples were analyzed for urea. The data thus obtained were used to calculate the urea dialysance, a concept analogous to clearance for human kidneys but independent of changing concentration gradients. Preliminary calculations suggest that at 300 ml./minute of blood flow through the dialyzer, the urea dialysance for the rotating drum is 230 ml./minute and for the twin coil 172 ml./minute. The use of Renkin's dialysance flow equation makes possible a comparison of urea transfer per unit surface area of cellophane

between the two machines. Further, an equation of Wolff's which relates dialysance of any solute to the volume of distribution cleared makes it possible to standardize patient size, blood flow, dialysis time, and arrive at a predicted drop in blood urea nitrogen. Such calculations, based on clinical dialyses, will be presented. In addition, certain operating characteristics of the twin coil machine such as pressures, resistances and dynamic volumes have been measured. With priming volumes of 1,000 ml. of bank blood, dynamic volumes may increase by 500 ml. or more, which must come from the patient's circulating volume.

Improvements in the design of the coil were suggested by the data and incorporated into the newer models. Repeated measurements justify the use of the calculations and data described for the purpose of designing and testing more efficient hemodialyzers.

HEMODYNAMIC ALTERATIONS DUE TO ATROPINE. POSTULATION OF A PERIPHERAL EFFECT. *Joseph N. Berry, William L. Gleason and Henry D. McIntosh.* Dept. of Medicine, Duke Univ. School of Medicine, Durham, N. C.

Hemodynamic alterations of hyperventilation were studied before and after administration of atropine. In five subjects in the supine position and in four subjects in the upright position, stroke index was unchanged by hyperventilation alone since increases in rate and cardiac index were proportionate. With the patients in both positions, atropine produced a greater increase in rate (73 per cent supine, 70 per cent upright) than in cardiac index (28 per cent supine, 0 per cent upright), resulting in a fall in stroke index (27 per cent supine, 40 per cent upright). The addition of hyperventilation in atropinized subjects (both positions) produced a further proportionate increase in rate and cardiac index, failing to alter the stroke index. The combination of atropine and hyperventilation was considerably less effective (by 47 per cent supine, 33 per cent upright) in increasing the cardiac index than hyperventilation alone, despite a greater rate increase.

Atropine decreases stroke index more with the patient in the upright than in the supine position. Hyperventilation, which normally maintains stroke index in both postures, fails to overcome this effect of atropine, suggesting inability of the atropinized subject to maintain an adequate central reservoir. It is postulated that atropine has a peripheral effect in decreasing venomotor tone.

EFFECT OF THIOURACIL ON THE PARTITION OF CHOLESTEROL BETWEEN SERUM AND LIVER. *Maurice M. Best* and Charles H. Duncan.* Univ. of Louisville School of Medicine, Louisville, Ky.

In an effort to produce experimental hypercholesterolemia in the rat, induction of hypothyroidism has been employed as an adjunct to cholesterol feeding. The observation that in animals receiving thiouracil higher levels of serum cholesterol developed than in those in which the thyroid was destroyed by iodine[131] suggested that thiouracil might exert a hypercholesterolemic effect independent of its suppression of thyroid activity. To test this hypothesis 0.5 per cent thiouracil was added for a two-week period to the diet of athyreotic rats. The mean serum cholesterol in the group fed thiouracil was 94 ± 9 as compared to 71 ± 7 mg./100 ml. in the control group ($P < .01$). In a similar study, except that 1 per cent cholesterol was incorporated in the diet, the mean serum cholesterol in the group fed thouracil was 131 ± 24 as compared to 107 ± 9 in the control group that was not fed thiouracil ($P < .05$). In both studies liver total cholesterol was lower in the group fed thiouracil, but the difference was not statistically significant.

The effect of thiouracil on hepatic synthesis of cholesterol from carbon-14 acetate, and on the partition of the labelled cholesterol between liver and serum was studied in the athyreotic rat. Two hours after its administration, the incorporation of C^{14} acetate into liver cholesterol was not significantly different in the two groups. However, in the group fed thiouracil the concentration of labelled cholesterol in the serum was higher than in the control group, 135 ± 41 compared to 81 ± 24 cpm./ml. ($P < .05$). These results indicate that an effect of thiouracil on the partition of cholesterol between liver and serum is responsible in part for its hypercholesterolemic effect.

EFFECT OF EXPERIMENTAL HYPERTENSION ON THE DEVELOPMENT OF PYELONEPHRITIS. *N. C. Brackett and C. M. Smythe.** Medical College of South Carolina, Charleston, S. C.

The causal relationship between chronic pyelonephritis and hypertension has been clearly

recognized for at least twenty years. Increased appreciation of the frequency of chronic urinary tract infections among hypertensive subjects created curiosity concerning the effect of hypertension on the development of pyelonephritis. An answer to this question would take years of study of a large group of patients and so an experimental approach was designed. Male Wistar rats weighing approximately 150 gm. were fed a diet of rabbit chow and given 0.5 per cent saline solution to drink. During the experimental period body weights doubled. Arterial pressures were measured by tail plethysmography. Animals were rendered hypertensive by wrapping one kidney in cellophane. Three groups were studied: controls, sham operated controls, and those with unilaterally wrapped kidneys. At the end of two months mean blood pressures in the three groups were: controls, 95 mm. Hg; sham operated controls, 94 mm. Hg; and those with unilaterally wrapped kidneys, 121 mm. Hg.

The animals were then inoculated intravenously with 1 ml. of a suspension of virulent E. coli containing 2 times 10^9 organisms/ml. Five animals died within twenty-four hours. Of the twenty rats remaining alive, in the control group four of 18 kidneys showed evidence of pyelonephritis, none of eight kidneys in the sham operated group, and one of the seven unwrapped kidneys in unilaterally wrapped group.

AUGMENTATION OF GANGLIONIC BLOCKING AGENTS WITH ORAL DIURETICS. *Allen C. Bullock and Ralph V. Ford.** Dept. of Medicine and Pharmacology, Baylor Univ. College of Medicine and the V. A. Hospital, Houston, Texas.

The possible potentiating effects of long-term oral diuretics upon antihypertensive drugs was investigated. The purpose was to observe the usefulness of chlorazinil and chlorothiazide in potentiating the effects of mecamylamine. It was postulated that the amount of mecamylamine required for therapeutic blockade would be substantially less if salt retention were decreased by the natriuretic agents. This was studied in twenty outpatients with similar diagnoses of hypertensive cardiovascular disease who had been followed up while receiving rauwolfia serpentina and mecamylamine, and whose optimal dosages had been fairly well established. The patients were of two groups of ten, one group receiving 300 mg. once and the other group twice daily of chlorazinil for three weeks. Chlorothiazide in comparable 500 mg. dosage once and twice daily was then substituted for three to four weeks. Only those with minimal renal disease and no overt failure were followed up. Blood pressures with the patient lying and standing, weight, blood urea nitrogen, white blood cell count and hematocrit were obtained, and mecamylamine dosage adjusted weekly. All patients received 400 mg. rauwolfia serpentina daily.

In eleven patients both diuretics potentiated the effect of mecamyalmine, requiring a reduction to maintain optimal blockade. There was little or no change in the requirements of nine patients. The conclusion was that chlorazinil and chlorothiazide have non-specific and limited use in the management of hypertension.

MORPHOLOGICALLY CHARACTERISTIC CHROMAFFIN REACTING CELLS IN DIGITAL AND EXTREMITAL SKIN OF MAN. *G. E. Burch** *and John H. Phillips, Jr.* Dept. of Medicine, Tulane Univ. School of Medicine, and Charity Hospital of Louisiana at New Orleans, La.

During our search for cells in digital tissues as local humoral factors partially responsible for local control of peripheral vascular tone, we were informed by Adams-Ray that he and Nodenstam had noted a chromaffin-reacting cell in tissues of man and animals. This cell manifests the classical "chromaffin reaction" with bichromate compounds (Orth's solution). Its morphologic and tinctorial characteristics, observed in preparations with Orth's solution and Sveki stain, differed from those of the mast cell, which it resembles when observed in conventional histologic preparations. Our extension of studies by Nodenstam and Adams-Ray has shown convincingly that these are not mast cells and that the chromaffin granules are located within the characteristically long, narrow, eel-like cells. They contain elongated, pale staining nuclei surrounded by cytoplasmic protrusions of pale staining material, with red to bluish red granules demonstrable on Sveki staining. The cells are irregularly distributed around blood vessels, nerves, hair follicles and sebaceous glands, and are more prevalent in toe tips than in finger tips. The fact that catechol amines, such as epinephrine and norephinphrine, as well as hydroxytyramine, 5-hydroxytryptamine and other related compounds, react positively to chromaffin-staining would suggest a possible

significant role of these cells in humoral regulation of tone of peripheral blood vessels.

RATES OF TRANSFER OF RB^{86}, K^{36}, NA^{24}, NA^{22}, CL^{36} AND CL^{35} ACROSS THE PERICARDIUM OF NORMAL DOGS. *G. E. Burch* and C. T. Ray.** Dept. of Medicine, Tulane Univ. School of Medicine, and Charity Hospital of Louisiana at New Orleans, La.

Rates of transfer of electrolytes and water across the pericardium have heretofore received little attention. When these were observed for several electrolytes, simultaneously, in twelve normal dogs, the unidirectional transfer per minute for Rb^{86} was 1.9 per cent of that present in the pericardial cavity initially, for Na^{24} 1.2 per cent, and for Cl^{36} 0.9 per cent. Corresponding bidirectional transfers per day were 9.5 mEq. K^{39} (assuming Rb^{86} traces K^{39}), 242 mEq. Na^{23} and 173 mEq. Cl^{35}. Mass rates of transfer were constant. When pericardial fluid was hypotonic, a net absorption of water from the pericardial sac resulted.

If the pericardial capillary bed of the dog (surface area about 400 $cm.^2$) is assumed to represent, functionally, the average capillary bed of the body of man (surface area 5,000 M^2), then the average rate of daily bidirectional simultaneous transfer of Na^{23} for the body is about 1,530 pounds, of K^{39} 102 pounds, and of Cl^{35} 1,680 pounds. Thus immeasurable changes in transfer rates across capillaries can be associated with large net changes in mass of electrolytes. The pericardium, therefore, is an extremely active transfer surface.

STUDIES OF ADRENAL CORTICAL SUPPRESSION BY AMPHENONE IN PATIENTS WITH SECONDARY HYPERALDOSTERONISM. *Sidney Blair Chenault, Jean H. McNeil, Willard Starnes, Mattie Gautney and S. Richardson Hill, Jr.** Dept. of Medicine and Univ. Hospital, The Medical College of Alabama and Medical Service, V. A. Hospital, Birmingham, Ala.

The therapeutic usefulness of amphenone has been limited by undesirable side effects. The present investigation was undertaken to assess the toxic and metabolic effects of small amounts of amphenone administered intravenously to patients with secondary hyperaldosteronism. The patients studied had marked fluid retention as the result of either cirrhosis of the liver, Kimmelstiel-Wilson syndrome or congestive heart failure, and failed to respond to the usual therapy. Amphenone was administered intravenously for up to twenty-four days. In one patient, beginning ten days after therapy, there was a two-fold increase in sodium excretion, marked diuresis, and glucocorticoid suppression. Heart valvular obstruction to blood flow prevented diuresis in another patient although urinary aldosterone levels were decreased within twenty-four hours from 73 to 12 μg. per twenty-four hours. Patients with cirrhosis of the liver did not tolerate the administration of even small amounts of amphenone because of semi-stupor.

Adrenal cortical suppression can be accomplished by amphenone administered intravenously in small amounts without severe toxic manifestations, providing severe hepatic disease is not present. With this technic approximately ten days are required for effective diuresis and glucocorticoid suppression. Altered circulatory dynamics may preclude a diuresis even though aldosterone levels have been reduced to normal.

EFFECT OF NITROGEN MUSTARD AND THIO-TEPA ON WOUND HEALING. *J. Harold Conn, Samuel M. Leb and James D. Hardy.** Dept. of Surgery, V. A. Center and Univ. of Mississippi Medical Center, Jackson, Miss.

The rationale for the use of chemotherapeutic drugs in palliation of cancer is based upon their cytotoxic and growth inhibiting effect on rapidly proliferating cells. Because of these effects it is important to know their influence on wound healing before they are used during the immediate postsurgical period. An experiment was designed to compare the effects of nitrogen mustard and Thio-TEPA on wound healing in dogs. Standard 5 cm. gastrotomies were made and closed with one layer of non-absorbable sutures. Ten dogs were used as controls. During the first three days postoperatively, ten dogs were given nitrogen mustard (0.4 mg./kg.) and ten received Thio-TEPA (2.0 mg./kg.). Dogs were sacrificed on the seventh postoperative day. The stomach was excised and after removal of sutures the gastrotomy wound was disrupted with air pressure. The disruption pressure was measured by a mercury manometer. The mean bursting pressure in the control group was 94.4 mm. Hg; in the nitrogen mustard group, 96.5 mm. Hg; and in the Thio-TEPA group, 93.6 mm. Hg. Sections of these wounds were also examined histologically. It is concluded that when nitrogen mustard and Thio-TEPA are

given in the usually recommended dosage during the immediate postoperative period, wound healing is not interfered with in dogs.

DETERMINATION OF REDOX ACTIVITY OF LEUKOCYTES AS A DIAGNOSTIC AID IN DISSEMINATED LUPUS ERYTHEMATOSUS. *C. David Cooper, William R. Felts, Thomas McP. Brown and Ruth Wichelhausen.** Dept. of Medicine, The George Washington Univ. School of Medicine, and Arthritis Research Unit, V. A. Hospital, Washington, D. C.

A metabolic alteration in leukocytes, demonstrated by depression of oxidation-reduction (redox) activity, has been reported in patients with acute disseminated lupus erythematosus. Studies were undertaken to determine the specificity of this reaction, prior to identification of the factor responsible for this altered metabolism.

The redox activity of leukocytes from 167 persons was studied. Normal values were obtained in 145, which included acute and chronic diseases, as well as fifty-nine normal subjects as controls. Depressed redox activity was found in twenty-two: seventeen clinically had L.E.; five were receiving hydralazine. Of the seventeen, seven had L.E. cells demonstrable at the time of initial study. Subsequently, L.E. cells developed in five; two had positive biopsies; three continued with a clinical course compatible with L.E., but L.E. cells were not found. Of the five patients taking hydralazine, four had symptoms of hydralazine reaction. Symptoms and depressed redox reverted to normal when hydralazine was withdrawn. In patients with L.E., treatment with steroids caused restoration of depressed redox to normal.

It is suggested that depression of redox activity is specific for disseminated lupus erythematosus and the hydralazine reaction, and could serve as a useful clinical adjunct in diagnosis.

A TREATMENT FOR CARDIAC SHOCK. *Jack W. Crowell and L. G. Hornsby.* Dept. of Physiology and Biophysics, Univ. of Mississippi Medical Center, Jackson, Miss.

The circumflex branch of the left coronary artery was ligated at its origin in sixty-seven dogs. Thirty-two of the animals fibrillated within thirty minutes and could not be used in this study; however, thirteen animals treated thirty minutes before ligation with 25 mg./kg. potassium iodoacetate, twelve animals untreated, and ten animals treated thirty minutes after ligation with 25 mg./kg. potassium iodoacetate were available for study. Only four (33 per cent) of the untreated animals survived for twenty-four hours and one (8.3 per cent) survived for three weeks. Ten (77 per cent) of the pretreated animals survived for twenty-four hours and seven (54 per cent) survived for three weeks. Seven (70 per cent) of the post-treated animals survived for twenty-four hours, and four (40 per cent) survived for three weeks.

The hypodynamic action of the ventricle following coronary occlusion is the resultant of two factors: (1) direct loss of the contractile elements and (2) "systolic stretch." Iodoacetate-poisoned muscle exhibits contracture and this contracture is potentiated by anoxia. By proper dosage it is possible to cause contracture of the ischemic area only, and this contracture prevents for a time the deleterious action of "systolic stretch" because the iodoacetate-poisoned ischemic muscle maintains a tension similar to that developed by healthy muscle during systole.

METABOLIC EFFECTS OF 9-ALPHA-FLUORO-16 ALPHA-HYDROXYL-DELTA-1 HYDROCORTISONE. *G. W. Curd and C. L. Spurr.** V. A. Hospital and Dept. of Medicine, Baylor Univ. College of Medicine, Houston, Texas.

An antiphlogistic steroid, 9-alpha-fluoro-16 alpha-hydroxyl-delta-1 hyrdocortisone, was studied by metabolic balance technics in two patients taking a diet analysed for sodium, potassium chloride, calcium, phosphorus and nitrogen. These diets, containing 50 mEq./day sodium and 75 and 93 gm. of protein, were eaten for forty days and analysis of the excreta begun after ten days equilibration. The steroid was given orally as the free alcohol in doses of 42 mg./day to a patient with systemic lupus erythematosus stabilized on prednisone 25 mg./day, and a dose of 82 mg. to a similarly controlled patient with lymphoblastic leukemia. Analytical periods were five days with one analytic period before and after administration of the halogenated steroid and four periods (twenty days) during medication with the test steroid. The results of mean balance calculations, on a daily basis, for the 42 mg. and 82 mg./day doses of halogenated steroid were: Sodium (−) 10.0, (−) 15.7 mEq./day; potassium (−) 5.4, (−) 26.0 mEq./day; chloride (−) 15.3, (−) 20.0 mEq./day; calcium (−) 0.88 gm., (+) 0.83

gm./day; phosphorus (+) 0.43, (+) 1.60 gm./day; nitrogen 0.0 gm. and (−) 3.0 gm./day. On prednisone therapy the patients were in positive balance, 3 and 7 gm./day, respectively. During the twenty-one-day study the body weight loss was 4.0 and 5. 0 kg., respectively. Renal function tests, glomerular filtration rate (inulin, Cr), renal plasma flow, Tm (PAH) showed only a decrease in renal plasma flow of 18 and 35 per cent, as compared to measurements the day prior to administration of halogenated steroid. The levels of glucose and plasma electrolytes remained stable. Negative electrolyte balance is a major factor in weight loss. The clinical status of both patients was controlled throughout the study.

CLINICAL AND PATHOLOGICAL FEATURES OF INFLUENZA-ASSOCIATED DEATHS, LOUISIANA, 1957. *L. F. Dietlein, J. Walsh, W. Pelon, W. J. Mogabgab* and G. E. Burch.* Dept. of Medicine, The Tulane Univ. of Louisiana School of Medicine, the New Orleans V. A. Hospital, The Charity Hospital of Louisiana at New Orleans, and the Louisiana State Department of Health, New Orleans, La.

From July to November, 1957, approximately eighty deaths could be attributed directly or indirectly to "Asian" influenza, and more than half of these occurred during the height of the epidemic in September. The majority of the patients (70 per cent) were ill only a week; a number of them, however, ran more rapid, fulminating courses. An autopsy was performed in twenty-nine (62 per cent) of forty-seven intensively investigated cases, and Asian strain virus was isolated antemortem or postmortem in three of these; others exhibited highly suggestive serologic and/or epidemiological evidence of infection. Bacterial pneumonia was the most frequent complication (59 per cent) with resistant Staphylococcus aureus the most common offender. Most of the pneumonias were severe fulminating bronchopneumonias. Five of the six obstetrical deaths were due to extensive bacterial pneumonitis and/or septic shock. Most of these occurred during the fifth month of gestation. Other associated conditions included chronic pulmonary disease, cardiovascular disease and chronic alcoholism. Pathological examination of the lungs revealed a purulent pneumonitis in most cases, but interstitial pneumonitis and hyaline membranes were found in a few instances. Areas of denuded bronchial mucosa with submucosal edema were also found in most specimens, and resembled the changes observed in biopsy material from acute influenza cases.

EARLY EFFECTS OF THYROTROPIN ON PBI^{131} RELEASE AND ON PLASMA IODIDE^{131} DISAPPEARANCE. *William P. Deiss, Jr.,* Patrick J. O'Shaughnessy and James O. Wynn.* V. A. Hospital, and Department of Medicine, Duke Univ. School of Medicine, Durham, N. C.

Thyroid stimulating hormone (TSH) stimulates thyroidal hormone release, iodide uptake, and growth. The sequence of these events and the mechanisms involved are not clear. These studies were designed to evaluate the first two parameters of TSH activity simultaneously in euthyroid subjects given I^{131}. PBI^{131} was determined after separation of iodide by anion exchange resin. Total plasma radioactivity minus PBI^{131} was assumed to be $iodide^{131}$.

TSH given twenty-four hours after administration of radioiodide caused prompt release of PBI^{131}, frequently beginning within thirty minutes, and by four hours in all but one of eighteen patients. It was not until twelve to thirty hours after administration of TSH, however, that a stimulus to thyroidal uptake of plasma iodide was noted, as reflected by increased plasma iodide disappearance rate. These observations indicate that hormone release precedes stimulation of plasma iodide uptake. Not only was there no immediate stimulus to thyroidal uptake, but a distinct "slowing" of uptake was apparent in nine of thirteen subjects, lasting for varying periods up to eighteen hours after administration of TSH. The mechanism of this slowing is not yet clear but it appears that it represents a period of decreased trapping of circulating iodide, perhaps due to increased availability of intrathyroidal iodide from stimulated deiodinase activity following administration of TSH.

THE RELATION OF GAMMA GLOBULIN TO INFECTION. *Harold L. Dobson, William Fahlberg, Dean Dukes and Ellard M. Yow.** Dept. of Medicine and Microbiology, Baylor Univ. College of Medicine, Houston, Texas; *and Jack Turner*, Odessa, Texas.

Fifty patients with disturbances in gamma globulin levels have been studied clinically and by means of serum electrophoresis and immunologic technics. Frequent bacterial infection,

usually due to gram-positive cocci, has been the most frequent complication. In two instances, increased susceptibility to viral infection has been noted.

Gamma globulin disturbances may be classified into primary and secondary defects. The primary defects are those for which no etiologic factor is evident. These may be sub-divided into agammaglobulinemia, hypogammaglobulinemia, and dysgammaglobulinemia. Agammaglobulinemia and some of the hypogammaglobulinemias are probably inborn errors in globulin metabolism and represent generalized immunologic arrest. The rest of the hypogammaglobulinemia and the dysgammaglobulinemia patients are probably examples of acquired immunologic deficiencies. The secondary disturbances include nephrosis, lymphoid leukemia, multiple myeloma, liver disease and chronic wasting illness. In the first two named there is usually a diminution in gamma globulin levels while in the rest there is an elevated gamma level which apparently does not function effectively in protecting against infection. It is our belief that these disturbances represent molecular diseases in the formation of gamma globulin secondary to genetic factors and altered reactivity of the reticuloendothelial system.

KINETOCARDIOGRAPHIC CHANGES AS THE RESULT OF MITRAL COMMISSUROTOMY. *E. E. Eddleman, Jr.** Dept. of Medicine, Medical College of Alabama, and the Medical Service of the V. A. Hospital, Birmingham, Ala.

Low frequency precordial movements (kinetocardiograms) were recorded before and after mitral commissurotomy in a selected group of patients. Postoperatively six patients not only had a reversion of the precordial movements toward normal but a striking clinical improvement which lasted two years. Five patients improved clinically during the first postoperative year but deteriorated during the second year often to a status worse than that noted preoperatively. The precordial movements did not change after surgery, which suggested that the hemodynamics were not altered significantly by the procedure even though a technically satisfactory valvulotomy was accomplished. Three patients were improved after commissurotomy and the precordial traces did not change. The traces from one patient with associated aortic insufficiency reverted from the pattern of a predominant mitral stenosis to that of aortic insufficiency. Two patients had only mitral insufficiency at surgery and both kinetocardiographic patterns revealed features of mitral insufficiency rather than of mitral stenosis. Kinetocardiographic traces appear useful in detecting major valvular heart lesions. In addition it appears in some instances that the hemodynamics of mitral stenosis can be completely reversed by mitral surgery. Kinetocardiograms also may give some information as to the eventual prognosis of the patient as well as aid in the selection of patients for surgery.

HYPERVOLEMIA AND APPARENT ANEMIA IN PATIENTS WITH ACUTE GLOMERULONEPHRITIS. *S. Eisenberg.* Medical Service of the V. A. Hospital, Dallas, Texas, and the Dept. of Internal Medicine of the Univ. of Texas Southwestern Medical School, Dallas, Texas.

Previous studies of blood volume alterations in persons with glomerulonephritis have yielded conflicting results and are subject to the following criticisms: (1) failure accurately to classify the types of nephritis, and (2) the questionable assumption that the dilution of intravenously administered dyes accurately reflects changes in blood volume.

Seven patients with serologically proved acute, poststreptococcal glomerulonephritis were studied. Radiochromium-labelled erythrocytes were employed as a reference, from which red cell mass was measured and total blood and plasma volumes were calculated. Clinical features included edema, venous hypertension and dyspnea. The measurements were repeated following spontaneous diuresis. The results showed (1) a 29 per cent increase in blood volume ($p < .001$) and a 38 per cent increase in plasma volume ($p < .001$); hematocrit and hemoglobin concentration were significantly decreased, but red cell mass was unchanged; and (2) following diuresis total blood and plasma volumes returned to normal, as did the hematocrit and hemoglobin concentration; red cell mass remained constant. These data indicate that there is selective expansion of the plasma space in acute glomerulonephritis. This contrasts sharply with the pattern of blood volume expansion in congestive heart failure, which includes a significant and consistent increase in red cell mass. The apparent anemia in acute glomerulonephritis is a dilution phenomenon.

SOME ENDOCRINE, RENAL AND NUTRITIONAL FACTORS GOVERNING MAGNESIUM METABOLISM. *Leonard*

P. Eliel, William O. Smith, Carl Thomsen and Josephine Hawrylko.* Oklahoma Medical Research Foundation, Medical Service, Veterans Hospital, and Dept. of Medicine, Univ. of Oklahoma School of Medicine, Oklahoma City, Okla.

The effects on magnetism metabolism of parathormone, acetazolamide, calcium and phosphate loading, protein deprivation, and vitamin D have been studied in man, using the metabolic balance technic. Two of four patients with hypoparathyroidism exhibited hypomagnesemia. The administration of parathormone resulted in: (1) disappearance of hypomagnesemia and hypocalcemia, and (2) parallel changes in urine magnesium and calcium, i.e., an initial drop followed by rises to values exceeding control levels. Administration of vitamin D likewise produced parallel urine changes in a hypoparathyroid patient with normal serum magnesium. Acetazolamide caused disappearance of tetany and prompt phosphorus diuresis, but only minor changes in serum and urine calcium and magnesium. Severe tetany appeared soon afterwards in association with a marked drop in serum magnesium. Intravenous calcium and phosphate loads were followed by falls in serum magnesium attributed to intracellular migration of this ion. Intestinal absorption of magnesium was decreased by dietary protein deprivation.

These studies suggest that: (1) the blood level and renal excretion of magnesium are governed directly or indirectly by parathyroid activity, (2) hypomagnesemia may facilitate the appearance of hypoparathyroid tetany, (3) the serum magnesium concentration may share in the same physical-chemical relationships governing calcium and phosphorus concentrations, and (4) intestinal absorption of magnesium, like calcium, is affected by protein intake.

SIGNIFICANCE OF THE EXTRA-ADRENAL METABOLIC ACTIONS OF CORTICOTROPIN PEPTIDES. *Frank L. Engel.** Dept. of Medicine and Physiology, Division of Endocrinology, Duke Univ., Durham, N. C.

The pituitary tropic hormones are generally assumed to act exclusively on their target glands. However, we and others have found that oxycel and pure peptide ACTH share certain metabolic activities with growth hormone (STH) and melanophore-stimulating hormone (MSH) in both intact and adrenalectomized animals. Studies of products of chemical inactivation (alkali, H_2O_2 and cysteine) and of pepsin and chymotrypsin digestion as well as comparative metabolic potency measurements of ACTH, STH, TSH and MSH eliminate mutual contaminations as the basis for common activities. Correlations with structure indicate that the N-terminal serine of ACTH is necessary for adrenal ascorbic acid depletion (AAAD) and metabolic but not melanophore activities. Removal of ten "tail" amino acids by pepsin eliminates ketogenic but not AAAD or MSH activities. β-MSH with a seven amino acid sequence in common with β-ACTH but no N-terminal serine lacks AAAD and ketogenic activities.

The hypothesis is proposed that the specificity of ACTH is related more to its affinity for the adrenal than to its ability to stimulate specific metabolic reactions (steroidogenesis). When administered or secreted in excess or perhaps when modified chemically as a peptide it may stimulate metabolism of other cells in a manner analogous to its action on the adrenal cortex, with results determined by the specific functions of the cell.

METABOLISM OF STEROID HORMONES BY HUMAN ENDOCRINE TUMORS. *Lewis L. Engel and Billy Baggett.* The John Collins Warren Laboratories of the Huntington Memorial Hospital of Harvard Univ. at the Massachusetts General Hospital and the Dept. of Biological Chemistry, Harvard Medical School, Boston, Mass. *and Ralph I. Dorfman and Kenneth Savard.* Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

The availability of isotopically-labeled steroid hormones and their precursors makes possible direct experimentation on isolated human tissues. The findings obtained in this fashion may be correlated with data obtained from a study of urinary excretion patterns. This approach has been applied to the study of steroid hormone metabolism by two human testicular tumors of widely differing cell types. In the first, an interstitial cell tumor of the testis in a five year old boy, it was possible to demonstrate the formation from radioactive acetate of 4-androstene-3,17-dione, 11β-hydroxy-4-androstene-3,17-dione, 17α-hydroxyprogesterone, testosterone, adrenosterone and dehydroepiandrosterone. The formation of nineteen carbon steroids bearing oxygen substituents was wholly unexpected in view of the histological characterization of the tissue. In the second tumor, a highly malignant,

undifferentiated tumor of the testis in a three year old boy, the formation from acetate-1-C^{14} of labeled hydrocortisone, 11β-hydroxy-4-androstene-3,17-dione has been demonstrated. Hydrocortisone synthesis was consistent with the clinical picture and demonstrated the remarkable biochemical capacities of this undifferentiated tissue.

INTRACARDIAC DIMENSIONS, ANATOMIC AND DYNAMIC. *Doris J. W. Escher.* Montefiore Hospital, Divisions of Medicine and Diagnostic Radiology, New York, N. Y.

This paper presents a new technic for demonstrating and clarifying the complex anatomy of the intact heart. Chambers, valve positions and lines of blood flow are presented on the basis of their natural three dimensional, torsioned relationship and these views are then related to the four standard roentgen exposures in which the heart is normally positioned for clinical study. Use is made in this demonstration of a semi-radiolucent normal heart model which is catheterized and x-rayed, as is done during cardiac catheterization. Comparison is made between views of the model, in which areas are selectively opacified for delineation and similar views of clinical material in which flow tracts and valve positions were established during cardiac catheterization. In addition to the main consideration of a dynamically normal heart, some elucidation of the blood flow patterns in interarterial and interventricular septal defect has also been undertaken.

CHLOROTHIAZIDE IN THE MANAGEMENT OF EDEMATOUS STATES. *M. Jeanne Fairweather, John M. Lewis, Ralph V. Ford* and Don W. Chapman.** Baylor Univ. College of Medicine, Houston, Texas.

To determine the diuretic properties of orally administered chlorothiazide (diurol®) as compared with parenteral thiomerin, the following study was initiated. A series of twenty edematous patients, either cardiacs or cirrhotics, were studied. They were at bedrest, given 800 mg. sodium diet with a controlled water intake of 3,000 ml. each twenty-four hours. The dosage of digitalis and antihypertensive drugs remained constant throughout in those who were previously receiving them. The serum electrolyte levels and the twenty-four hour urinary volume and excretion of sodium were determined. Teleroentgenograms and electrocardiograms were obtained at the onset and completion of the study. Daily weights were recorded. After a three-day control period ten patients received 2,000 mg. of chlorothiazide orally each day for three days; the other ten patients received 2 cc. of thiomerin parenterally initially for three days. Another three-day control period followed, then the diuretics were reversed. Serum sodium, potassium, chloride, bicarbonate, blood urea nitrogen and hematocrit were analyzed on control day three, and drug day two of each three-day period.

The natriuresis and water diuresis is greater following the administration of chlorothiazide than thiomerin. In one patient with cirrhosis totally refractory to thiomerin a twenty-pound diuresis was obtained with chlorothiazide. Continued administration of chlorothiazide may lead to hypokalemia, hypochloremia and an elevation of CO_2; however, this is reversible with potassium chloride. Chlorothiazide potentiates the effect of hypotensive agents. Chlorothiazide has thus been found to be an effective relatively non-toxic oral diuretic.

17–21 HYDROXYCORTICOSTEROIDS IN LABOR AND DELIVERY. *Lee L. Farris, M. D. Turner, James D. Hardy* and Michael Newton.* Dept. of Surgery and of Obstetrics & Gynecology, Univ. of Mississippi Medical Center, Jackson, Miss.

Previous studies of plasma 17–21 hydroxycorticosteroid levels in obstetrical patients have shown a rise in the antepartal period and return to normal after delivery. The object of this investigation was to determine the plasma levels of 17–21 hydroxycorticosteroids at specific times during and after the physiological stress of labor and delivery. Fifteen normal women were selected at random for this study. All had normal, spontaneous labor; minimal analgesia and anesthesia were necessary. Blood samples were drawn from an antecubital vein at about the thirty-sixth week of pregnancy, during active labor, at delivery of the baby, immediately after delivery of the placenta, and one, four and twenty-four hours postpartum. Determination of 17–21 hydroxycorticosteroid material in the plasma was made by the methods of Nelson and Samuels and Bongiovanni. The following mean values for free and glucuronide conjugates of 17–21 hydroxycorticosteroids, expressed in μg./100 cc. were obtained, late pregnancy, 10.63; active labor, 14.71; delivery, 21.16; end of third stage, 26.50; one hour postpartum, 27.01; four

hours postpartum, 15.05; twenty-four hours postpartum, 11.04; cord blood, 3.37.

These results confirm previous findings of high plasma 17–21 hydroxycorticosteroid levels in pregnancy. A further rise is demonstrated during labor and delivery, reaching a maximum one hour after delivery. The levels reached are not as high as those found during and immediately after major surgical operations but they do suggest that labor and delivery are accompanied by increased activity of the adrenal cortex.

ANTI-TRYPTIC AND TRYPSINOGEN ACTIVATOR CONTENT OF THE PLASMA IN ACUTE PANCREATITIS. *Ira M. Goldstein, Max Butler, Marcel Patterson and Raymond Gregory.** Dept. of Internal Medicine and the John Sealy Memorial Laboratory for Clinical Research, Univ. of Texas Medical Branch, Galveston, Texas.

The present report deals with a study of the possible abnormal enzyme relationships in blood and other body fluids in an attempt to throw further light on the etiology of acute pancreatitis. These studies were made by a modification of the method of Anson and Mirsky employing the enzyme-substrate system of trypsinogen, casein and an activating amount of trypsin. Control values were established in eight normal adults and in twenty hospitalized patients without evidence of pancreatic disease. The same study was made on seven patients with acute pancreatitis, the diagnosis of which had been established by clinical symptoms and confirmed by high serum amylase values.

There was no evidence that the serum of normal subjects or patients with acute pancreatitis had the capacity to activate trypsinogen. The results clearly demonstrate an increased amount of antitryptic activity in the plasma of patients with acute pancreatitis. It is believed that the changes observed are the results and not the cause of the pancreatitis. The possibility that the increased antitryptic activity of the plasma may be related to the recovery of the patient is being further investigated.

DOES INTERNAL MAMMARY LIGATION INCREASE ARTERIAL FLOW TO THE MYOCARDIUM? *James C. Griffin, Jr.,' James D. Hardy** and *M. D. Turner.* Dept. of Surgery, Univ. of Mississippi Medical Center, Jackson, Miss.

The purpose of this experiment was to demonstrate and evaluate the distribution of blood flow to the epicardium and myocardium following ligation of the internal mammary arteries. The internal mammary arteries were cannulated, methylene blue injected, and a color movie made of the immediate passage of the dye from the artery to the pericardium through a large number of very small vessels. Ligation of the artery was performed unilaterally on the left and right side in two series of dogs. These dogs were opened later through a sternal-splitting incision and the gross size of the arteries compared. The internal mammary artery of the dogs that had been previously ligated was cannulated and a saturated solution of KCl solution stained with methylene blue was injected. Two control series were performed and we found that 0.1 cc. of the KCl solution perfused through the coronaries would result in cardiac arrest or fibrillation.

Communications between the arteries of the pericardium and coronaries were demonstrated in a small number of dogs, but we believe that the amount of blood supplied to the coronaries through these communications is very limited.

STUDIES ON THE SPINAL FLUID AND SERUM PROTEIN PATTERNS IN PATIENTS WITH DIABETES MELLITUS. *William J. Hammack, Willard R. Starnes and S. Richardson Hill, Jr.** Dept. of Medicine and Univ. Hospital, The Medical College of Alabama and the Medical Service, V. A. Hospital, Birmingham, Ala.

Studies have been undertaken to characterize the serum and spinal fluid protein in thirty-eight patients with diabetes mellitus and eighteen normal subjects. Simultaneous electrophoresis of the serum and spinal fluid were performed using the Spinco model "R" paper electrophoresis system and the results were calculated both in per cent of total protein and in milligrams. In diabetic patients without degenerative complications the protein patterns of the serum and spinal fluid were within normal limits. Those with diabetic neuropathy had a normal serum protein pattern but an elevated spinal fluid total protein, consisting of milligram increases in each fraction especially in the gamma globulin. Patients with diabetes mellitus and persistent proteinuria had a normal spinal fluid total protein and an elevated alpha-one and gamma globulin fraction. The serum of these patients was characterized by a decreased albumin and increased alpha-two and gamma globulin fraction. The increase in the alpha-two fractions may result from increased glycoprotein which is

associated with this component. The changes in the patients with diabetic neuropathy suggest the presence of other active mechanisms in addition to a generalized increase in vascular permeability.

FURTHER STUDIES OF HUMAN ADRENAL VEIN BLOOD: SECRETION OF ESTROGENS AND 17-KETOSTEROIDS. *James D. Hardy* and Virginia B. Ward.* Dept. of Surgery and Univ. Hospital, Univ. of Mississippi Medical Center, Jackson, Miss.

In an earlier communication, measurements of hydrocortisone secretion in man were reported. The data were obtained by means of left adrenal vein blood samples collected over a timed period at laparotomy. The rate of hydrocortisone secretion during the stress of operation was found to be of the order of 111 mg./twenty-four hours; and under normal conditions, perhaps 34 mg./twenty-four hours.

Such studies have now been extended to include measurement of adrenal venous estrogen and 17-ketosteroid concentrations, as compared with peripheral venous plasma estrogen and 17-ketosteroid levels before, during and following surgery. In fifteen subjects during operation the mean 17-ketosteroid level in adrenal vein plasma was 203 gamma/100 ml.; in peripheral blood during operation it was 87.6 gamma. The peripheral plasma levels of 17-ketosteroid substances did not differ materially before, during and following surgery. The estrogen levels also were higher in adrenal vein blood than in peripheral blood. As with the 17-ketosteroids, the peripheral estrogen levels were not materially affected by major surgery. In one patient so studied, both the estrogen and the 17-ketosteroid levels in ovarian vein plasma were slightly lower than those in adrenal vein blood, but considerably higher than those in peripheral venous plasma. These findings re-emphasize the roles which the adrenal glands and the ovaries may play in the natural history of estrogen-dependent tumors.

MEGALOBLASTIC ANEMIA ASSOCIATED WITH ANTICONVULSANT THERAPY. *Robert C. Hartmann* and John M. Flexner.* Dept. of Medicine, Vanderbilt Univ. School of Medicine, Nashville, Tenn.

In the past few years approximately twenty-five instances of megaloblastic anemia have been recorded in patients treated with diphenylhydantoin, primidone and phenobarbital, alone or in various combinations. A case is presented in which severe megaloblastic anemia developed after two years of treatment with diphenylhydantoin and phenobarbital. Due to food allergies and idiosyncrasies, sources of folic and ascorbic acids were virtually eliminated from the diet. Nutritional studies revealed deficiencies of folic acid and vitamins A, C and B_{12}. However, except for the megaloblastic anemia there were no clinical manifestations of nutritional deficiency.

Complete hematological remission was obtained with the administration of only 500 μg. of folic acid orally per day given for a thirty-day period. This remission has been maintained for five months despite continuation of anticonvulsant drugs without further folic acid therapy. The megaloblastic anemia may result from the combination of nutritional deficiencies and possible pharmacodynamic inhibition of folic acid metabolism by the anticonvulsant drugs. In certain of the previously reported cases there is some suggestion of dietary inadequacy. A prerequisite background of nutritional deficiency may explain why megaloblastic anemia develops only rarely in a patient receiving anticonvulsant drugs.

INTRALUMINAL PRESSURE CHANGES IN THE PHARYNX AND ESOPHAGUS DURING DEGLUTITION IN MAN. *N. C. Hightower, Jr.** Laboratories for Clinical Investigation and Research, Scott and White Clinic, Temple, Texas.

Sequential pressure changes in the pharynx, pharyngoesophageal junction, esophagus and esophagogastric junction have been recorded in fifteen subjects during deglutition using three small, open-tip catheters in tandem. In the pharynx, resting pressure is slightly positive (2 to 8 cm. H_2O). Within 0.1 to 0.3 seconds after initiation of deglutition a sharp peak of positive pressure (40 to 60 cm. H_2O) occurs and usually is followed by a short negative wave. The positive pressure wave traverses the pharynx in 0.3 to 0.5 seconds. At the pharyngoesophageal junction, resting pressure is high (20 to 30 cm. H_2O), and the characteristic pressure change with deglutition is diphasic (negative then positive). In the esophagus, resting pressure is negative (-2 to -8 cm. H_2O). As the peristaltic contraction passes down the esophagus an initial brief negative wave is followed by a gradual increase in pressure, terminating in a large positive wave usually reaching 100 cm. H_2O. At the esophagogastric junction, resting pressure is high

(10 to 20 cm. H_2O). Deglutition produces a gradual reduction (relaxation), and then a gradual increase in pressure (contraction) as the peristaltic wave passes over the terminal esophagus. Deglutition pressures correlate well with anatomic structures and mechanical events.

MEMBRANE ELECTRICAL POTENTIALS IN EXPERIMENTAL VENTRICULAR TACHYCARDIA AND FIBRILLATION. *Charles E. Hogancamp and Milton Kardesch.* Dept. of Medicine, Washington Univ. School of Medicine and the Washington Univ. Medical Service, V. A. Hospital, St. Louis, Mo.

The intracellular microelectrode was utilized to study the depolarization-repolarization process in guinea pig hearts with induced ventricular arrhythmias. Hearts with a ligature about the AV groove were placed in oxygenated Tyrode's solution. Recordings were made from superficial ventricular cells. Application of aconitine crystals to the ventricular surface regularly produced fibrillation. In most of the preparations a transient period of ventricular tachycardia preceded the development of fibrillation. During the period of tachycardia, alternation in the amplitude of action potentials was frequently seen. In any single preparation electrical alternation could be recorded from several cells, although not all cells exhibited this phenomenon. Within ten to fifteen minutes ventricular fibrillation ensued. Comparison of action potentials from cells of various areas revealed variations in their rate and amplitude. As time elapsed, complete depolarizations became less frequent and the pattern of action potentials of small amplitude at the rate of 500 to 900 per minute resulted. These studies suggest that electrical alternans seen in the electrocardiogram may be related to alternation in amplitude of action potentials in a great number of single myocardial cells. They also indicate that in ventricular fibrillation, single myocardial cells participate in disorganized electrical activity in the form of irregular and incomplete action potentials.

THE TESTOSTERONE CONTENT OF HUMAN SPERMATIC VEIN BLOOD. *N. Hollander and V. P. Hollander.* Univ. of Virginia, School of Medicine, Charlottesville, Va.

A method has been developed for the estimation and recovery of microgram quantities of ketonic steroids from plasma. This permits analysis for testosterone and similar substances in 2 to 5 ml. plasma.

Spermatic vein blood was obtained during inguinal herniorrhaphy or orchiectomy for carcinoma of the prostate. C-14 testosterone was added to plasma to facilitate chemical studies. Steroids were extracted from plasma and the dinitrophenylhydrazones were formed according to the procedure of Reich. Chromatography, using alumina, was performed. The fraction containing the added counts was rechromatographed. Constant count to color ratio permitted estimation independent of manipulative losses. Identity was confirmed by conversion of the dinitrophenylhydrazone to the free steroid with pyruvic acid and chromatography. In seven patients with hernia the testosterone level in spermatic vein blood varied from 0 to 1 μg. per ml. plasma, and decreased with increase in age. The level in four patients with carcinoma of the prostate was approximately half that of normal subjects of comparable age. Further studies are in progress to confirm this difference. Testosterone was not found in peripheral blood by this method.

EFFECT OF POTASSIUM REPLETION ON THE RENAL STRUCTURAL CHANGES AND THE RENAL CONCENTRATING DEFECT PRODUCED BY POTASSIUM DEPLETION IN RATS. *Walter Hollander, Jr., Robert W. Winters, John Bradley, Malcolm Holliday, T. Franklin Williams, Jean Oliver and Louis G. Welt.** Dept. of Medicine and Pediatrics, Univ. of North Carolina School of Medicine, Chapel Hill, N. C.; Dept. of Pediatrics, Univ. of Pittsburgh, Pittsburgh, Penna.; and Renal Research Unit, Overlook Hospital, Summit, N. J.

The reversibility of the renal concentrating defect and the renal structural abnormalities associated with potassium depletion in rats were studied (1) during eight days immediately following rapid potassium repletion, and (2) after eight months of potassium repletion. From the beginning of acute repletion (accomplished with frequent gavage feedings of potassium chloride during thirty-six hours) (a) the concentration of potassium in dry fat-free skeletal muscle returned to normal within two days; (b) the concentrating defect subsided rapidly and was no longer statistically significant within three days; (c) the swelling and hyperplasia in the collecting tubules in the outer medulla decreased, as did the droplets in the collecting tubules of the inner medulla, but none of these abnormalities had disappeared within eight days.

Eight months after repletion with stock diet

(a) the concentration of potassium in dry fat-free skeletal muscle had returned to control levels; (b) renal concentrating ability was normal; (c) the blood urea nitrogen was not elevated; (d) kidney tissue was bacteriologically sterile;(e) the acute collecting duct lesions had disappeared but there were fibrous scars and cystic dilatation of collecting tubules not present in controls. This study supports the contention that permanent renal damage may result from an acute episode of potassium depletion.

SERUM TRANSAMINASE FOLLOWING VENTRICULOTOMY. *Hector S. Howard and William A. Neely.* Jackson Dept. of Surgery, Univ. of Mississippi Medical Center, Jackson, Miss.

Serum transaminase levels, determined daily for five days in five dogs subjected to sham thoracotomies, were found to rise to a maximum level on the first to second postoperative day. The same dogs were later subjected to right ventriculotomies through right thoracotomies. All ventriculotomies were full thickness and were 3 cm. in length. Again daily serum transaminase determinations were obtained for five days. These values were then statistically compared with the levels obtained after the sham left thoracotomy. The average level after thoracotomy alone was 52 units. After thoracotomy and ventriculotomy the average level was 118 units. Although the series was small, each animal served as his control, and the spread of the data was such that the difference was significant (P greater than 0.05 and less than 0.10). The levels after ventriculotomy were of the same order of magnitude as those observed clinically following myocardial infarction. These studies demonstrate a significant elevation of the transaminase released following cardiac incisions, which must be recognized to avoid false inferences during the postoperative period.

THE ANABOLIC STERCOBILIN OF DISORDERED ERYTHROPOIESIS. *G. Watson James, III* and Lynn D. Abbott, Jr.* Laboratory for Clinical Investigation, Dept. of Medicine and Dept. of Biochemistry, Medical College of Virginia, Richmond, Va.

Oral feedings of 1 gm. of N^{15}-labeled glycine have been given to two normal subjects and to six patients with various disorders of the hematopoietic system to study the patterns of fecal stercobilin labeling in relation to hemin labeling during the first twelve to sixteen days of hemin synthesis. The stercobilin tagged at this time is considered to come from a source *not* that of the destruction of circulating erythrocytes during this period.

Two patients with megaloblastoid anemia who were unresponsive to either vitamin B_{12} or folic acid; two hypoplastic and one aplastic anemia subjects with elevated fecal urobilinogen determinations; and one patient with chronic granulocytic leukemia showed greatly increased amounts of fecal stercobilin which appeared to be derived from a source not that of the circulating erythrocytes. The data available from our studies at the present time strongly suggest a disturbance of a fundamental mechanism of pigment synthesis in a number of seemingly unrelated hematopoietic disorders. The abnormality appears to be an enhancement of an anabolic synthesis of stercobilin greater than the 10 to 20 per cent anabolic synthesis observed in normal subjects.

ISOLATED JEJUNAL LOOPS IN MONKEYS AS AN ASSAY METHOD FOR HUMAN INTRINSIC FACTOR. *P. C. Johnson, T. O. Hodges, T. B. Driscoll and Stewart Wolf.** Dept. of Medicine and Surgery, V. A. Hospital and Univ. of Oklahoma Medical School, Oklahoma City, Okla.

Chow has suggested that there is some degree of species specificity for the absorption of vitamin B_{12}. Gastrectomized rats have served as a convenient assay animal for intrinsic factor from some sources but Niewig et al. have shown that they fail to absorb vitamin B_{12} when it is mixed with either hog or human gastric juice. On the other hand, rat gastric juice does promote vitamin B_{12} absorption in man. The present study concerns fractions separated from human gastric juice and assayed for intrinsic factor activity. The monkey was found to be a suitable test animal. A new technic for testing was devised which had substantially less effect on the nutritional state of the monkey than gastrectomy. A loop of jejunum was resected and exteriorized with its original blood supply intact. The continuity of the remaining intestine was then reestablished by an end-to-end anastomosis. Tests were performed at weekly intervals by instilling into the loop 0.02 or 0.12 μg. of Co-60 vitamin B_{12} with or without a dialysed preparation of human gastric content shown to contain intrinsic factor by assay with pernicious anemia patients. Twenty-four hours after instillation,

and daily for five days, radioactivity over the liver was counted, using a 4 by 3 inch plastic scintillation counter. From these data vitamin B_{12} absorption was calculated. In twenty-two control observations it was found that no significant absorption followed instillation of Co-60 vitamin B_{12} alone into the jejunal loop. In twenty-one test observations Co-60 vitamin B_{12} was mixed with 3 to 25 mg. amounts of dialysed and lyophilized human gastric content. Under these circumstances absorption of approximately one-half of the quantity of tracer absorbed by an intact monkey after oral administration of the Co-60 vitamin B_{12} was consistently observed.

DISSEMINATED COCCIDIOIDOMYCOSIS APPARENTLY CURED WITH AMPHOTERICIN B. *Margaret S. Klapper.* Dept. of Medicine, Medical College of Alabama, and School of Dentistry, Univ. of Alabama, Birmingham, Ala.

A thirty-four year old white woman with extensive musculoskeletal coccidioidomycosis of ten years' duration was treated with amphotericin B, a new antifungal antibiotic. The diagnosis was made by the isolation of Coccidioides immitis on repeated occasions, and the presence of a positive precipitin test and a high complement fixation reaction toward this organism. At the initiation of therapy the patient had thirty-five draining sinuses and abscesses of the buttocks and thighs, with involvement of the sacrum and left ilium, ischium and femur. She was febrile, emaciated, anemic, and had a leukocytosis. One gram of amphotericin B was given orally four times daily for fourteen months. Improvement was apparent within two weeks. All lesions were healed within three months, and weight, temperature, white count and hemoglobin had all returned to normal. Eighteen months after initiation of therapy all lesions remain healed, and the patient is in good health. The drug was well tolerated, and at no time was there evidence of untoward hepatic, renal or hematopoietic effects.

OBSERVATIONS ON THE CIRCULATORY DYNAMICS IN PATIENTS WITH CHRONIC LUNG DISEASE. *K. H. Kilburn and H. O. Sieker.** Dept. of Medicine, Duke Univ. School of Medicine and the V. A. Hospital, Durham, N. C.

To investigate the relationship between cardiac and pulmonary insufficiency observed frequently in patients with chronic lung disease, the effects of mechanical and pharmacological stimuli on the heart and lung were studied. Pulmonary arterial pressure, "wedge" pressure, cardiac output and blood gases were determined at rest, during exercise, 100 per cent oxygen breathing and infusion of isoproterenol and acetylcholine. Results in ten patients with chronic lung disease and eight patients with primarily heart disease were compared with a normal control group.

In contrast to normal subjects, exercise raises pulmonary arterial pressure [mean difference (m.d.) 11 mm. Hg], increases cardiac output slightly (m.d. 0.27 L./minute/sq. meter) and decreases blood oxygen saturation in patients with chronic lung disease. Breathing 100 per cent oxygen lowers pulmonary arterial pressure (m.d. 4.7 mm. Hg) without affecting cardiac output. Isoproterenol raises pulmonary arterial pressure (m.d. 3.2 mm. Hg) and increases cardiac output (m.d. 0.47 L./minute/sq. meter). In patients with heart failure it lowers pulmonary artery pressure while increasing cardiac output. Acetylcholine infusion, which decreases pulmonary arterial pressure in normal subjects, produced a drop in patients with chronic lung disease but prolonged infusion raised this pressure without altering cardiac output.

Patients with chronic lung disease cannot decrease the pulmonary vascular resistance in response to mechanically or pharmacologically induced increases in cardiac output. They can decrease pulmonary vascular resistance in response to increased oxygen tension of the blood.

NATURE OF THE METABOLIC ACCELERATION INDUCED BY SINGLE LARGE DOSES OF DESICCATED THYROID. *Laurence H. Kyle,** *John J. Canary and Richard J. Meyer.* Dept. of Medicine, Georgetown Univ. Medical Center, Washington, D. C.

Recent emphasis on the immediate and intense effect of triiodothyronine has reinforced the concept that desiccated thyroid hormone is slow to act and prolonged in duration of effect. Evidence to the contrary led to comparison of the type of metabolic acceleration induced by single, large, physiologically comparable doses of desiccated thyroid (DT), thyroxin (T_4) and triiodothyronine (T_3) in two normal and five myxedematous subjects. Indices of stimulation included the basal metabolic rate, blood cholesterol, protein-bound iodine (PBI), pulse rate

and nitrogen balance. Increases in the basal metabolic rate and pulse rate were nearly identical as regards both latent period and duration of response with all three compounds. The PBI rose out of proportion to the degree of metabolic acceleration with T_4 and showed little change with T_3 but its response to DT fitted well with other indices of stimulation. No difference was noted in the speed or degree of reduction of elevated serum cholesterol levels. The onset, intensity and duration of negative nitrogen balance, a sensitive and reproducible measure of metabolic acceleration, was quite similar with all three drugs. In general, variation of all indices of metabolic acceleration was as marked in the individual subjects as in the three thyroid hormones.

This study offers no evidence for a long-acting component in desiccated thyroid hormone. The nature of the metabolic acceleration fits best with the concept that this preparation is composed of, or rapidly converted to, triiodothyronine and thyroxin.

EFFECTS OF TWO STEROIDAL "ALDOSTERONE ANTAGONISTS" UPON ELECTROLYTE EXCRETION. *Grant W. Liddle.** Dept. of Medicine, Vanderbilt Univ. School of Medicine, Nashville, Tenn.

Preliminary studies in adrenalectomized dogs indicated that two new synthetic steroids (having "spirolactone" structures at the 17-carbon) suppressed the renal response to aldosterone and desoxycorticosterone. Metabolic studies were then performed in eight patients with congestive heart failure, two with nephrosis, two with Addison's disease, and in seven normal subjects.

Results: (1) In adrenalectomized dogs and Addisonian patients maintained on high sodium diets alone, the spirolactones had no significant effect on electrolyte excretion. (2) In adrenalectomized dogs and Addisonian patients pretreated with aldosterone or desoxycorticosterone, the spirolactones opposed the sodium-retaining and potassium-losing effects ordinarily seen with aldosterone and desoxycorticosterone. (3) All the effects of aldosterone and desoxycorticosterone which were tested were reversed by treatment with the spirolactones. Whereas aldosterone and desoxycorticosterone caused retention, the spirolactones caused urinary loss of sodium, chloride and water. Whereas aldosterone and desoxycorticosterone caused increased excretion, the spirolactones caused decreased excretion of potassium, titratable acid and ammonia. (4) In doses of 1 gm. daily the spirolactones were useful clinically as diuretic agents. (5) The spirolactones had no significant effect on urinary corticoid or aldosterone levels.

Without settling the question of whether or not salt-losing steroids occur naturally, these results substantiate the *concept* of "salt losing steroid."

THE DIVERSE DISTRIBUTION OF RED CELLS AND ALBUMIN WITHIN ANATOMIC REGIONS OF THE KIDNEY. *L. S. Lilinefield,** *N. A. Lassen and J. C. Rose.* Cardiovascular Research Laboratory, Dept. of Medicine, Georgetown Univ. Medical Center, Washington, D. C.

Recent reports have restimulated interest in the relationship between red cells and plasma within the kidney. This study concerns relative distribution of red cells and albumin in the cortex, inner medulla and papilla of sixteen dog kidneys. Cr^{51} red cells and I^{131} albumin were injected systemically, and the renal pedicle was ligated one hour later. Only animals maintaining arterial pressures at 125 to 180 mm. Hg were included. Kidney sections were weighed, and Cr^{51} and I^{131} activity was determined and compared with activities of arterial blood. Red cell volume averaged 6.1, 6.6, and 3.7 ml. per 100 gm. cortex, inner medulla, and papilla, respectively. Corresponding calculated albumin volumes of distribution were 23.5, 34.3, and 37.6 ml. per 100 gm. (assuming tissue albumin concentration equal to plasma concentration). Arterial hematocrits averaged 46.5 (range 32.0 to 58.8). Ratio of kidney section "hematocrit" to arterial hematocrit averaged 0.49, 0.35, and 0.19, respectively. When summed, red cell and albumin volumes of distribution total an absurdly high figure for intravascular volume. Concentrating mechanisms have been suggested for medulla and papilla, but not for cortex. Therefore, at least in the cortex, there exists a sizeable *extravascular* albumin pool. Its magnitude implies high extravascular protein concentration in the cortex.

PRECORDIAL MOVEMENTS IN RELATION TO AURICULAR CONTRACTION. *John Lowder, Lloyd L. Hefner and Donald Harrison.* Dept. of Medicine Medical College of Alabama, Birmingham, Ala.

The motions of the precordium occurring between the onset of auricular excitation and of ventricular excitation have been studied in twenty-two normal subjects and in sixty-eight

subjects with various types of cardiac disease. All normal subjects display an initial forward rightward motion followed by a leftward backward movement. These motions are observed in patients with heart block following isolated P waves. They are absent in subjects with auricular fibrillation. The initial forward motion is markedly increased in amplitude in most patients with cor pulmonale, while the second backward motion is exaggerated in those with mitral stenosis. They therefore are respectively attributed to contraction of the right and left auricles. Patients with various types of cardiac disease may display exaggeration of either or both of these movements. Their diagnostic value, therefore, appears to be limited to the occasional clinical problem involved in the distinction between mitral stenosis and cor pulmonale.

PHYSIOLOGIC SIGNIFICANCE OF THE SECRETION OF INSULIN INTO THE PORTAL CIRCULATION: COMPARISON OF THE METABOLIC EFFECTS OF INSULIN AFTER ADMINISTRATION BY INTRAPORTAL AND SYSTEMIC ROUTES. *Leonard L. Madison and Roger H. Unger.* Dept. of Internal Medicine, The Univ. of Texas, Southwestern Medical School, Dallas, Texas.

Since endogenous insulin is secreted into the portal circulation and traverses the liver, its metabolic effect and distribution may differ from exogenous insulin which first enters the systemic circulation. To investigate this the effects of glucagon-free insulin on the magnitude of hypoglycemia and on the magnitude of increase in peripheral arteriovenous (A-V) glucose difference were compared in eight dogs after intraportal and peripheral injections. Profound differences in metabolic effects result from the different routes of administration. The degree of hypoglycemia was identical but peripheral injection resulted in significantly greater ($p = <.01$) A-V glucose difference (mean 7 mg. per cent) than portal injection (4.6 mg. per cent). This indicates a greater hepatic and smaller peripheral effect of intraportally administered insulin. Hepatic binding of I^{131}-labeled insulin after both routes of administration was compared in fifty rats. Peak hepatic binding was significantly greater ($p = <.01$) after endoportal administration (51 per cent of dose) compared to peripheral administration (30 per cent).

The data suggest that intraportal secretion of insulin has physiologic importance. The initial transhepatic passage of all endogenous insulin results in a greater hepatic effect and a smaller peripheral effect than insulin injected into the systemic circulation. This physiologic balance between hepatic effect and peripheral effect is *not* duplicated by peripherally injected exogenous insulin.

INFLUENCE OF INTRINSIC FACTOR ON THE COMBINING OF VITAMIN B_{12} BY "RECEPTOR-PROTEINS" OF TISSUES. *O. Neal Miller and Fred M. Hunter.* Dept. of Biochemistry and the Nutrition and Metabolism Unit of the Dept. of Medicine, Tulane Univ. School of Medicine, New Orleans, La.

It has been reported recently that intrinsic factor (IF) concentrates stimulate the uptake of radioactive vitamin B_{12} by rat liver slices. This work has been extended to the use of homogenates. It was found that homogenates of liver combine more vitamin B_{12} in the presence than in the absence of IF. Free B_{12} was removed by dialysis against 100 volumes of isotonic KCl. When these same homogenates after incubation and dialysis were centrifuged at 25,000 times G, the broken cell membranes, nuclei and mitochondria were sedimented and the supernatant fluid was removed by decantation. Both the sediment and the supernatant fractions were counted in a well-type scintillation counter. The supernatant fraction showed an increase in combined B_{12} in the presence of IF whereas the sediments counted the same regardless of whether or not IF was added. It was concluded that IF was exerting its action on liver slices by facilitating absorption of vitamin B_{12} rather than combining B_{12} to the outer surface of cell membranes of the slices. Homogenates have been fractionated with $(NH_4)_2SO_4$ and a fraction obtained, "B_{12}-receptor-protein," which combines B_{12} in the presence of IF. Receptor-proteins have been found in the brain, heart, kidney, muscle, spleen, lung, intestine and serum.

FACTORS RÉSPONSIBLE FOR HYPERPNEA DURING HEAVY EXERCISE. *Jere H. Mitchell, Brian J. Sproule and Carleton B. Chapman.** Cardiopulmonary Laboratory of the Dept. of Internal Medicine, Univ. of Texas Southwestern Medical School, Dallas, Texas.

The cause of hyperpnea of muscular exercise has never been adequately explained. To elucidate the mechanisms, arterial pO_2, pH, pCO_2 and "central blood volume" in normal men were studied during treadmill exercise at

maximal oxygen intake level. Determinations were made during the last minute of a two-and-a-half minute exercise period. Respiratory rate increased from 18 ± 4 (resting) to 40 ± 12; ventilation (BTPS) from 9.70 ± 1.19 to 88.98 ± 14.51 L.

Arterial pO_2, measured polarographically, was 87 ± 9 mm. Hg at rest and 88 ± 12 during exercise. Per cent saturation was 97.1 ± 3.1 resting and 94.7 ± 2.6 during exercise. Decreased oxygen saturation is explained by arterial pH changes during exercise. Resting arterial pH, measured directly, was 7.40 ± .04; that during exercise 7.19 ± .09. Arterial pCO_2, calculated from CO_2 content and pH, was 39.3 ± 3.9 resting and 37.2 ± 5.5 during exercise. Venous pCO_2, however, increased markedly. "Central blood volume" (Hamilton's method) increased from 1.71 ± 0.32 resting to 3.49 ± 0.83 L. during exercise. The results are directly opposed to Bannister's unsupported suggestion that changes in arterial pO_2 and pCO_2 are responsible for hyperpnea during heavy exercise. Changes in arterial pH, central blood volume and especially in venous pCO_2 are more likely determinants.

ALTERATIONS IN RENAL HEMODYNAMICS IN PATIENTS WITH THE "DUMPING SYNDROME." *George C. Morris, Jr.,* Lazar John Greenfield and George L. Jordan, Jr.* Dept. of Surgery, Baylor Univ. College of Medicine, Houston, Texas.

An interesting postprandial circulatory disturbance sometimes follows surgical procedures which alter normal gastric drainage. The objective signs in the dumping syndrome include tachycardia and hemoconcentration as well as electrocardiographic and electroencephalographic changes which have been interpreted as a reflection of myocardial and cerebral ischemia. It has been postulated that these changes are in direct response to a sudden contraction of blood volume incident to a loss of plasma water within the intestine.

Discrete renal function studies in symptomatic postgastrectomy patients revealed a statistically significant postprandial increase in renal blood flow in twelve patients who manifested the dumping syndrome. In view of these findings, previous physiologic concepts of the dumping syndrome may need revision.

INTRAVENOUS INFUSION OF PLASMIN (FIBRINOLYSIN): STUDY OF ITS TOXICITY AND FIBRINOLYTIC ACTIVITY IN THIRTY-THREE PATIENTS. *Kenneth M. Moser.* Georgetown Univ. School of Medicine and District of Columbia General Hospital, Washington, D. C.

Demonstration that intravenous plasmin (fibrinolysin) can dissolve intravascular thrombi in dogs and rabbits has suggested its use in human thromboembolic disease. These studies assess its toxicity and fibrinolytic activity in man. Thirty-six infusions of highly purified human plasmin, preactivated with streptokinase, were given to thirty-three patients. Dosages ranged from 30,000 to 50,000 units, with infusion time averaging three hours. During twenty-four hours following infusion, prothrombin time and content, factor 7, plasma recalcification time and hematocrit remained virtually stable. There was transient, slight to moderate lowering of fibrinogen in nine patients and factor 5 in six. In no patient did hemorrhagic phenomena develop including thirteen receiving anticoagulants simultaneously. Postinfusion electrocardiograms and urinalyses were unchanged. Blood pressure showed no significant deviation for twenty-four hours following infusion. A febrile response of 1°F. to 4°F. occurred in twelve patients, and above 4°F. in three. Temperature elevation usually appeared from six to eight hours postinfusion and persisted for eight to ten hours. Enhanced fibrinolytic activity, assayed using a standard fibrinogen-thrombin clot, was noted in thirty-three patients. Activity appeared within two hours, usually peaked at four to six hours, and declined sharply by ten hours. Sixteen patients showed an apparent activity "rebound" at twenty-four hours.

These studies suggest that intravenous plasmin can induce significant intravascular fibrinolytic activity without prohibitive toxicity.

IDIOPATHIC ACQUIRED HEMOLYTIC ANEMIA ASSOCIATED WITH A CHEMICAL (INSECTICIDE) DEPENDENT POSITIVE COOMBS' (ANTIGLOBULIN) TEST. *E. E. Muirhead,* Margaret Groves, Ruth Guy, E. R. Halden and R. K. Bass.* Dept. of Medicine and Pathology, The Univ. of Texas Southwestern Medical School, Dallas, Texas.

A thirty-four year old farmer with pancytopenia, purpura, splenomegaly and a strongly positive direct Coombs' test improved markedly following splenectomy. Twenty-one months later he returned with severe hemolytic anemia (hemoglobin 5 gm. per cent). He had frequent contacts with insecticides, particularly "hep-

tachlor" and "dieldrin." Immunologic studies demonstrated: (1) Strongly positive direct Coombs' test when the erythrocytes were collected and maintained at 37° to 40°C., (2) a cold agglutinin effective slightly below 37°C. and with strong avidity at room temperature; (3) apparent panagglutination of erythrocytes of the same Rh and ABO type by means of the indirect Coombs' test when the patient's serum was collected and separated at room temperature; failure to remove this phenomenon by chilling in contact with patient's erythrocytes collected and separated at 37° to 40°C.; (4) specificity of the patient's serum, apparently isoimmune, when the serum was collected and separated at 37° to 40°C. as shown by the finding of erythrocytes from 4 of 140 donors tested which gave a negative or plus-minus indirect Coombs' test; (5) a strongly positive antiglobulin (Coombs') test which was dependent on the patient's serum collected warm and the two insecticides to which the patient had been exposed. The latter was repeatedly demonstrated with the compatible erythrocytes, thus suggesting a chemical (insecticide) etiology for the anemia.

OSMOTIC DIURESIS AS A TEST FOR DIABETES INSIPIDUS. *H. V. Murdaugh, Jr.* Dept. of Medicine, Duke Univ. School of Medicine, and V. A. Hospital, Durham, N. C.

It has been implied that T^dH_2O (ADH-dependent) quantitatively exceeds T^cH_2O when GFR is normal. If correct, this would mean that T^cH_2O would not be measurable in the absence of ADH, even though it is ADH-independent.

Accordingly, T^cH_2O ($C_{O_{sm}}$ − volume) was measured during osmotic diuresis obtained with hypertonic dextrose given until heavy glucosuria developed and standardized to GFR by inulin clearance. Normal subjects, patients with diabetes insipidus, and patients thought to have diabetes insipidus were studied. In normal subjects $T^cH_2O = 4.75 \pm 0.91$ (standard deviation, normal of 14) ml./minute/1.73 sq. meter body surface area or 3.70 ± 0.87 ml./100 ml. GFR. Volume exceeded $C_{O_{sm}}$ in all five patients with diabetes insipidus giving values of −0.6 to −13.8 ml./100 ml. GFR (C_{H_2O}), but positive values (T^cH_2O) were obtained after pitressin® administration. Two patients with abnormal Hickey-Hare tests, previously treated with pitressin, were found to have normal T^cH_2O and then found able to concentrate urine normally without pitressin. Some patients with diabetes insipidus were uncomfortable during the procedure, and in one the plasma osmolality increased to 410 mOsm/L.

It is suggested that osmotic diuresis can be used as a physiological test for diabetes insipidus. These findings support the contention that T^dH_2O is quantitatively greater than T^cH_2O.

DURATION OF ANEMIA NECESSARY FOR DEVELOPMENT OF CARDIAC HYPERTROPHY IN RATS. *Tom D. Norman and Robert D. McBroom.* Dept. of Pathology, Univ. of Mississippi Medical Center, Jackson, Miss.

As part of a study of the effect of anemia upon the heart an experiment was planned to determine how soon experimental hypertrophy would occur in moderately anemic rats. Ten rats received phenylhydrazine hydrochloride (40 mg./kg. body weight) intraperitoneally every other day for fifteen days, ten received the drug for twenty-four to twenty-seven days, and eleven were treated similarly for fifty to fifty-three days. The mean hemoglobin levels ranged from 7 to 11 gm. (after the first week of treatment) except for a terminal rise in the experiment of longest duration. The hearts were opened, washed, blotted dry, and weighed at the time of sacrifice. The relationship of heart and body weights was established in each group and in a group of non-anemic rats, by the equation $\log Yc = \log a + b \log X$ and plotted on log-log paper. The lines thus formed showed no apparent difference between the control and fifteen-day group, slightly higher values in the twenty-four to twenty-seven day experiment, and much higher values in the fifty to fifty-three day group. A significant difference was shown between mean heart weights of the control and twenty-four to twenty-seven day group when the compared rats were limited to a 10 gm. weight range. It is concluded that significant cardiac hypertrophy occurred within four weeks in rats made moderately anemic with the administration of phenylhydrazine.

A DIRECT RENAL TUBULE EFFECT OF STROPHANTHIDIN ON ELECTROLYTE EXCRETION IN THE CHICKEN. *Jack Orloff* and Maurice Burg.* National Heart Institute, Bethesda, Md.

Strophanthidin exerts a direct effect on renal tubule transport of Na^+, H^+ and K^+ ions in the chicken. Although others had demonstrated

a renal effect of glycosides, it has not been possible to exclude the influence of changes in hemodynamics and filtered load of electrolytes. Chickens possess a renal-portal circulation. The peritubular concentration of a test substance can be maintained higher on the experimental than on the contralateral control side. Since changes in filtrate composition are equal and bilateral, unilateral changes in urine composition on the experimental side are due to alterations in tubule function.

The administration of strophanthidin into one leg of a chicken induces a prompt unilateral increase in Na^+ excretion and urine pH. If initially elevated, K^+ excretion decreases. If initially low, K^+ excretion either is unaffected or rises. The increase is less than observed when Na^+ excretion is elevated with sodium sulfate. The marked increase in Na^+ excretion and associated fall in the excretion of K^+ and H^+ ions following strophanthidin are presumably due to inhibition of the transport system whereby Na^+ is reabsorbed in exchange for K^+ and H^+ ions.

PANCREATIC DISEASE: EFFECTS UPON THE LIPIDS AND PANCREATIC ENZYMES OF THE SERUM. *Harold H. Orvis, Richard C. Fowler and John M. Evans.** Dept. of Medicine, The George Washington Univ. School of Medicine, Washington, D. C.

A study of serum lipoproteins and pancreatic enzymes in thirteen patients with pancreatic disease was undertaken to evaluate the role of the pancreas in lipid metabolism. Ten of the patients had acute pancreatitis, one had chronic pancreatic insufficiency, and two had been pancreatectomized for cancer. In most of the patients serum total lipid and cholesterol were normal. However, two of the patients had gross hyperlipemia upon admission for pancreatitis. The percentage of cholesterol in the beta lipoprotein fraction was increased in nine of ten patients with acute pancreatitis, the peak elevation occurring within one to eight days from onset; and, in contrast, was low in the patients with chronic pancreatic disorders. Similarly, the serum lipase was elevated in all patients with acute pancreatitis, was low in the patient with pancreatic insufficiency, and absent in the patients after pancreatectomy. The peak values for lipase preceded those for beta lipoprotein cholesterol in patients with pancreatitis studied serially. Serum amylase was normal in two patients after pancreatectomy. Serum tributyrinase was elevated in only one patient with acute pancreatitis but was otherwise normal in the presence of pancreatic disease or after pancreatectomy.

On the basis of these findings it is concluded that pancreatic lipase may influence transport of lipoprotein cholesterol, that serum amylase may be normal after pancreatectomy, and that serum tributyrinase is an unsatisfactory indicator of pancreatic disease.

RENAL TUBULAR CHANGES IN ACUTE GLOMERULONEPHRITIS. *Alvin E. Parrish,** *John S. Howe and Mary F. Watt.* Dept. of Medicine and Pathology of The George Washington Univ. School of Medicine and the V. A. Hospital, Washington, D. C.

Tubular changes, although recognized, have not been emphasized in acute glomerulonephritis. The circulation of the kidney is such that with severe glomerular disease, when glomerular capillary lumens are diminished, tubular lesions would be anticipated. In twenty patients with acute glomerulonephritis, a correlation was attempted between the pathologic condition seen in needle biopsy material, renal functions (inulin, urea clearances and phenolsulfonphthalein excretion or Tm PAH), and the clinical course. Renal biopsy was performed initially in all patients and repeated in thirteen, one to three times. Inulin and PAH clearances and Tm PAH were determined in eleven patients, and repeated in eight of these two to three times. The patients have been followed up for a maximum of five years clinically and for three years by biopsy. All have shown tubular pathologic conditions at some time during their disease. Early, within the first two weeks, pyknosis and vacuolization were present in tubular cells. In two instances this was pronounced and associated with a clinical picture of anuria. Renal functions early show depression of phenolsulfonphthalein excretion, Tm PAH, and a low urinary specific gravity. Later, tubular dilatation became the predominant lesion. Tubular dilatation was not associated with decreased Tm PAH unless other abnormalities were also present. Tm PAH and inulin clearance seemed to be related in the acute stage of the disease.

FURTHER STUDIES ON THE 2060 VIRUS ISOLATED FROM PERSONS WITH MILD RESPIRATORY ILLNESSES. *W. Pelon and W. J. Mogabgab.** Dept. of Medicine, Tulane Univ. School of Medicine, New Orleans, La.

Previous investigations have shown that

neutralizing antibody to 2060 virus, isolated from Naval recruits with mild respiratory illnesses, was prevalent in the population of the Chicago area. A broad distribution of neutralizing antibody against this agent in the New Orleans area was also found; 50 per cent of randomly selected serums currently tested had titers of 1 to 40 or greater. In addition, 2060 was isolated from persons with mild afebrile illnesses who later demonstrated increments in neutralizing antibody to the virus. Recent studies have shown that 2060 was unrelated to Sabin's chimp rhinitis virus (ECHO 11), Harrington virus (ECHO 16) or the Cochrane virus. However, similar growth and cytopathogenic characteristics as well as features of the associated illness have suggested relationship to JH virus. Cross neutralization studies with the latter have confirmed this, but have also demonstrated antigenic differences, indicating that these are representative types of a larger group. Studies of the metabolic requirements of 2060 in monkey kidney cultures, and aspects of the associated clinical illness will be presented.

MUCIN OF HUMAN SYNOVIAL FLUID. *Ward Pigman, Edgar Gramling, Howard L. Holley* and David Platt.* Medical College of Alabama, Birmingham, Ala.

The mucins of human tissues comprise an important group of ill-defined biological substances which appear to be carbohydrate-protein complexes or compounds. The mucin of synovial fluid is precipitated by acetic acid and has been used for differentiating normal from arthritic synovial fluids. In the present paper studies of the composition of synovial mucin prepared from postmortem and arthritic synovial fluids are reported. These studies were made by electrophoretic analysis at pH 8.6, ionic strength 0.1, in veronal buffer. The addition of acetic acid apparently caused complete precipitation of hyaluronic acid, and the polysaccharide could not be detected in the supernatant. The redissolved mucin was always characterized by the presence of hyaluronic acid, albumin and an α-globulin, probably the α_2-globulin.

"Mucin" has been postulated to be almost wholly responsible for the viscosity of synovial fluid. The mucin obtained in the present work had a viscosity which was never more than 60 per cent of that of the original diluted synovial fluid, under comparable conditions. Synovial mucin seems to be an easily dissociable complex (salt), mainly of albumin and hyaluronic acid.

A STUDY OF THE MEANS BY WHICH EXERCISE INCREASES THE PULMONARY DIFFUSING CAPACITY FOR CARBON MONOXIDE. *J. C. Ross, R. Frayser and J. B. Hickam.** Dept. of Medicine, Duke Univ. School of Medicine, Durham, N. C.

It is well established that the diffusing capacity of the lung for O_2 and CO (D_{co}) increases during exercise, but the phenomenon is poorly understood. In normal subjects D_{co} depends largely on the size of the pulmonary capillary bed in contact with well ventilated alveoli. Conceivably, exercise might increase D_{co} by (1) effects secondary to increased cardiac output, such as enlargement of the pulmonary capillary bed, or (2) effects secondary to increased ventilation. To separate these factors, D_{co} (Filley) and cardiac output (dye method) were measured in normal recumbent subjects during rest, exercise, epinephrine infusion, and hyperventilation, both voluntary and on 5 per cent CO_2. In four subjects, exercise increased D_{co} (+79 per cent), cardiac output (+120 per cent) and ventilation (+170 per cent); while epinephrine infusion increased cardiac output (+90 per cent), but had little effect on ventilation (+20 per cent) or D_{co} (+17 per cent). In four additional subjects, voluntary and hypercapneic hyperventilation (+240 per cent and 270 per cent, respectively) increased D_{co} (+70 per cent and +50 per cent) with little change in cardiac output (+11 per cent and +32 per cent). These results suggest that the effect of exercise on D_{co} may depend much more on changes in ventilation than on changes in output. Increased amplitude and rate of ventilation may increase D_{co} by enlarging the capillary bed which is effectively ventilated or by improving distribution of air to the existing capillary bed.

COMPARISON OF INDOLE-3-ACETIC ACID AND ORINASE REGARDING HYPOGLYCEMIC EFFECT AND "PLASMA INSULIN ACTIVITY" IN JUVENILE AND ADULT DIABETES. *Holbrooke S. Seltzer.* Dept. of Medicine, The Univ. of Texas Southwestern Medical School, and V. A. Hospital, Dallas, Texas.

Indole-3-acetic acid (IAA), a physiological end-product of tryptophane metabolism, induces hypoglycemia in normal subjects and in patients with mild diabetes. Mirsky attributes this phenomenon to anti-insulinase activity. Conversely, orinase (tolbutamide) probably causes hypoglycemia by stimulating endogenous insulin secretion. The effects of these supposedly differently-acting substances on blood glucose and

"plasma insulin activity" (Vallance-Owen rat diaphragm method) were compared in severe (juvenile) and mild (adult) diabetics subjects. Administration of oral orinase (3 gm.) or IAA (100 mg./kg.) did not depress the blood sugar in five patients with juvenile diabetes withdrawn from exogenous insulin. Plasma insulin activity was undetectable both before and after drug administration. In ten patients with mild diabetes, maximal hypoglycemia was comparable after the administration of orinase (43 ± 11 per cent below fasting glucose value) and IAA (34 ± 11 per cent). However, the fasting plasma insulin activity demonstrable in these patients did not increase during the hypoglycemic response to either substance.

These data suggest that insulin-dependent hepatic mechanisms may underlie the acute hypoglycemic response to both compounds: orinase-released insulin, bound within the liver, could enhance hepatic glucose assimilation and decrease glycogenolysis. Liver insulinase inhibited by IAA may increase net intrahepatic insulin, with *in situ* tissue-binding and metabolic activity. In each case, increased insulin activity might be undemonstrable peripherally.

INFLUENCE OF GLYCOLYSIS ON DIABETIC LIPOGENESIS. *Marvin D. Siperstein and Violet M. Fagan.* Dept. of Internal Medicine, The Univ. of Texas Southwestern Medical School, Dallas, Texas.

It is now clearly established that the depressed synthesis of fatty acids in diabetes mellitus is secondary to the diminished glycolysis characteristic of this disease. Nonetheless, the specific cause of this lipogenic defect has remained obscure. Studies have therefore been undertaken in liver homogenates to determine the effect on diabetic lipogenesis of alternately repairing each of two glycolytic pathways—the Embden-Meyerhof route by addition of glucose-6-phosphate plus DPN, the hexosemonophosphate pathway with glucose-6-phosphate plus TPN. Reinstitution of Embden-Meyerhof glycolysis produced only slight (ten- to twentyfold) enhancement of lipogenesis in diabetic homogenates whereas repair of hexosemonophosphate glycolysis caused very marked stimulation of one hundred- to three hundredfold. Since hexosemonophosphate oxidation generates TPNH, another system capable of producing this cofactor, D-isoc trate and TPN, was substituted for hexosemonophosphate glycolysis. This system was also found to stimulate fatty acid synthesis in the diabetic.

It is therefore concluded that the lipogenic defect in diabetes is due primarily to deficiency of hexosemonophosphate glycolysis; TPNH is the deficient cofactor responsible for this lesion. Furthermore, these findings furnish a plausible explanation for diabetic ketosis, inasmuch as the TPNH lesion in lipogenesis would result in accumulation of the four carbon intermediates which are the precursors of ketone bodies.

EFFECTS OF ESTROGENS ON THE INCORPORATION OF C^{14} FORMATE INTO HUMAN BREAST CANCER. *H. H. Sky-Pack, S. Kofman, R. J. Winzler and S. G. Taylor, III.* Dept. of Biological Chemistry of the Univ. of Illinois School of Medicine and the Dept. of Medicine of Presbyterian-St. Luke's Hospital, Chicago, Ill.

The *in vitro* incorporation of C^{14}-formate into normal and neoplastic breast tissues, taken from patients with metastatic carcinoma of the breast, has been studied before, during and after a course of estrogen therapy. Normal and neoplastic breast tissues were obtained from the same person by biopsy, sliced with the aid of a Stadie-Riggs slicer, and alternate slices fixed for pathological evaluation. The remaining slices were incubated in a Krebs-Ringer's bicarbonate medium containing C^{14}-formate and non-labeled glucose. The incubations were terminated after an interval of five hours and the specific activities of the protein fractions determined. The results indicated a surprising consistency in C^{14}-formate uptake into normal breast tissues. The cancer tissues, on the other hand, showed widely varying incorporation rates and selective effects due to the hormone therapy. These effects were an increased or decreased rate of incorporation of C^{14} into the proteins with clinical progression or regression of the disease. There was a lack of correlation between the rate of C^{14}-formate incorporation and the total area of tumor cells or the amounts of DNA and RNA in these tissues. This seems to indicate that the large differences in uptake among breast tumors and following therapy may be due to metabolic changes. It is suggested that this technic may be useful in the early detection of tumor response to carcinolytic or carcinostatic agents.

RADIOSTRONTIUM METABOLISM IN MAN AND SR^{85} STUDIES IN CLINICAL INVESTIGATIONS. *Herta Spencer.* Montefiore Hospital, New York, N. Y.

The metabolism of radiostrontium (Sr^{85}) was compared with that of Ca^{45} and calcium. It was found that less strontium than calcium is

absorbed from the gastrointestinal tract, and that more strontium than calcium is excreted by the kidney. Enhancement of radiostrontium excretion could be achieved by raising the urinary calcium excretion through administering calcium intravenously and/or orally, either alone or in combination with ammonium chloride. The technic of Sr^{85} determinations in biological specimens is a simple and sensitive indicator of mineral metabolism, and has been extensively used in the study of patients with metabolic or neoplastic bone diseases and for the objective evaluation of various therapeutic agents. The metabolic effects of 17-ethyl-19-nortestosterone (nilevar), of 3-methoxy-16α-methyl-1,3,5 (10)-estratriene-16β,17β-diol (manvene) and of 17α-ethinyl-19-nortestosterone (norlutein) were studied with this tracer. Improvement of mineral metabolism was readily demonstrable by balances and Sr^{85} studies.

EXCRETION OF ALDOSTERONE IN NORMAL MEN AND WOMEN AND IN PATIENTS WITH TOXEMIA OF PREGNANCY. *L. L. Sulya, J. Slocum, M. D. Turner.* Dept. of Physiological Chemistry, *and J. E. Lindley,* Dept. of Obstetrics and Gynecology, Univ. of Mississippi Medical Center, Jackson, Miss.

The excretion of aldosterone in the urine of normal men, normal women and patients with toxemia of pregnancy was determined by the following procedure. The urine after acidification to pH 1 was extracted continuously for twenty-four hours and the extract purified as outlined by Ayres, Garrod, Simpson and Tait (1957). The purified residue was chromatographed successively with the systems chloroform-formamide and Bush's system C (Neher and Wettstein 1956). The aldosterone was eluted and determined spectrophotometrically after color development with blue tetrazolium. Analysis of the urine of thirteen normal men, mainly medical students, gave an average of 19.9 gμ. per twenty-four hours with a range of 8 to 33.5. Results with ten normal women (student nurses, technicians) were in the range of 8.8 to 30.7, with an average of 17.2 μg. per twenty-four hours. The difference is not statistically significant. These results are higher than reported by Ayres et al. who obtained an average of 11 μg. per twenty-four hours with a range of 4.6 to 23.5. Ten patients with toxemia of pregnancy excreted an average of 22.7 μg. of aldosterone during the first hospital day. The difference between this mean and the normal series is not significant. Medication and/or bedrest produced a significant reduction within twenty-four hours to an average of 12.7 μg.

EXCHANGE AND EQUILIBRATION CHARACTERISTICS OF POTASSIUM IN RHEUMATOID ARTHRITIS AND OTHER DISEASE STATES AS DETERMINED THROUGH THE USE OF POTASSIUM 42. *Ernest S. Tucker, III, Howard L. Holley,* William E. Martindale, Marshall S. Little and William L. Hawley.* Dept. of Medicine, Medical College of Alabama, and the Radioisotope Service of the V. A. Facility, Birmingham, Ala.

The observation that generalized muscular weakness is common in rheumatoid arthritis and characterizes states of hypopotassemia prompted these studies: (a) A comparison of the exchangeable K^{42} in rheumatoid subjects with patients having other types of chronic illness; (b) measurement of rates of diffusion of $K^{42}Cl$ from the intravascular compartment and into the urine in two groups of patients with rheumatoid arthritis, one symptomatically treated, the other receiving maximal ACTH stimulus to the adrenal glands; (c) observations similarly made in two dogs given steroid hormones or ACTH following intravenous administration of $K^{42}Cl$.

Twenty-four hours following the administration of 200 to 250 μc. $K^{42}Cl$ intravenously the exchangeable K, as mEq. K./kilo, in seven rheumatoid arthritic patients was not different from exchangeable K in nine other patients with chronic illnesses. In patients with rheumatoid arthritis exchangeable K was 45 $\pm$ 18.3 mEq./kilo. The disappearance rate of K^{42} from the blood stream was faster and the rate of secretion into the urine slower in rheumatoid subjects receiving maximal stimulus with ACTH for a short time after intravenous administration of K^{42}. This observation was most striking at thirty minutes when the urine concentration of K^{42}/K^{39} in untreated subjects was three times that of the treated subjects. Supplemental dog experiments suggest that this rapid loss probably results from equilibration with the extravascular compartment.

INHIBITION OF THYMOL FLOCCULATION BY NORMAL AND ICTERIC SERUMS. *Malcolm P. Tyor.* Dept. of Medicine, Duke Univ. School of Medicine and the V. A. Hospital, Durham, N. C.

Inhibitory factors have been demonstrated for most commonly used flocculation and turbidity tests, except the thymol flocculation test. The purpose of the present study was to determine

the presence of an inhibitory factor in normal and icteric serums.

The degree of flocculation of serums was measured by their turbidity ratio,

$$\frac{\text{48 hour turbidity units}}{\text{30 minute turbidity units}}$$

Strongly flocculating serum (turbidity ratio = 0.05) was diluted with serums which did not flocculate (turbidity ratios = 0.85 to 1.40); the range of dilutions was 3:1 to 1:3, respectively. The non-flocculating serums were obtained from twelve control subjects, seven jaundiced patients with primary liver disease, and seven jaundiced patients with pancreatic or biliary carcinoma. The mean turbidity ratios for the three groups at dilutions of 1:1 and 1:2 were most significant; control subjects = 0.12 and 0.33, patients with primary liver disease = 0.12 and 0.45, patients with extrahepatic obstruction = 0.37 and 0.79, respectively. When group means were compared, the t values of the extrahepatic group were significantly greater than those of the control group, $p = <0.01$. The two jaundiced groups were suggestively different, $p = <0.05$.

Inhibition of thymol flocculation by icteric serums from patients with neoplastic extrahepatic obstruction was significantly greater than that produced by serums from control subjects, and suggestively greater than that produced by serums from patients with primary liver disease.

ASIAN INFLUENZA. A CLINICAL STUDY. *John Walsh, Lawrence Dietlein, H. A. White, William Mogabgab,* William Pelon and George Burch.** Dept. of Medicine, The Tulane Univ. of Louisiana School of Medicine, New Orleans V. A. Hospital. The Charity Hospital of Louisiana at New Orleans, New Orleans, La.

This study deals with forty patients in whom the diagnosis of Asian influenza was established by virus recovery of fourfold or greater rise in the hemagglutination inhibition antibody titer of paired serums. Fatal cases are reported elsewhere. The clinical syndrome was rather typical of influenza of varying severity. Physical findings were sparse and non-specific. Relative bradycardia during the first two days of illness was noted in one-fourth of the patients. A normal or depressed leukocyte count was usual, although leukocytosis was encountered in uncomplicated influenza. Bacteriologic studies of nasopharyngeal, blood and sputum specimens revealed no abnormalities. Laboratory studies, including evaluation of hepatic, adrenal and renal function were within normal limits. One-fifth of the patients exhibited transient electrocardiographic changes consisting of inverted or diphasic T waves without rise in serum glutamic oxalacetic transaminase.

Of seven pregnant patients, one experienced premature labor with death of the fetus, one lost a full term infant at nine days of bacterial meningitis, and two had complicating pneumonia. There were seven patients with associated pneumonia. All were treated with antibiotics, and on the average, were febrile for only two days longer than those patients with simple influenza. There was one case of severe meningoencephalomyelitis with paraplegia followed by complete recovery.

OBSERVATIONS ON THE FUNCTIONAL STATE OF THE PULMONARY BLOOD VOLUME. *James V. Warren,* Joseph J. Combs and Gerald D. N. Bryant.* Dept. of Medicine, Duke Univ. School of Medicine, Durham, N. C.

In an effort to separate the dynamic and static components in the pulmonary blood volume, observations on twelve normal subjects have been carried out. Measurements of so-called "pulmonary blood volume" (Q value of Stewart) have been made under control conditions and during atropine-induced tachycardia. The rapid heart rate was associated with a 75 per cent higher mean cardiac output and a 24 per cent larger mean "pulmonary blood volume." In four subjects additional evaluation of total thoracic blood volume was made by another technic utilizing external radiation over the thorax following intravenous injection of radioactive iodinated serum albumin. Atropine tachycardia failed to produce changes indicative of altered blood content of the underlying lung.

These apparently disparate results are consistent with the thesis that at rest some pulmonary capillaries, although filled with blood, are perfused so slowly that they are not included in the initial circulation involved in the calculation of "pulmonary blood volume" by the dye technic. With increased cardiac output, the perfusion rate in these vessels was accelerated, and an apparent increase in pulmonary blood volume was obtained. Such a concept of stagnant flow through some pulmonary capillaries

is supported by the increased diffusion capacity of the lungs during the augmented cardiac output of exercise.

RESPIRATORY EFFECTS OF TOTAL PULMONARY DENERVATION. *Watts R. Webb and Hector S. Howard.* Jackson Dept. of Surgery, Univ. of Mississippi Medical Center, Jackson, Miss.

The following studies evaluate the results of total pulmonary denervation on pulmonary function. In initial experiments requiring the interruption of all cardiopulmonary accessory circulation, which incidentally denervated the heart and lungs, the dogs were found unable to maintain adequate spontaneous respiration. Similarly, six dogs with cardiopulmonary transplants were unable to breathe spontaneously. Transplants of the heart and one lung alone allowed relatively normal breathing. Eight of ten mediastinal dissections to denervate completely both the lungs and the trachea without transplantation, likewise led to respiratory failure. Pulmonary denervation in four dogs without tracheal denervation caused profound pulmonary ventilatory changes which, however, were compatible with survival. In staged denervations the physiologic effects of cervical vagotomy, thoracic vagotomy and cervicothoracic sympathectomies were recorded singly and in combinations. All three procedures were required to accomplish total denervation with respiratory insufficiency in eleven of fifteen animals. Some dogs died immediately; others gasped slowly as long as six hours before dying of respiratory failure.

These findings suggest vagal pathways to the medullary center other than through the cervical vagal trunk and that the "intrinsic periodicity" of the respiratory center, if existent, is inadequate without afferent impulses from the lung.

EFFECT OF TEMPERATURE UPON THE AMOUNT OF HERPES SIMPLEX VIRUS PRODUCED IN TISSUE CULTURE. *Clayton E. Wheeler.** Dept. of Dermatology, School of Medicine, Univ. of Virginia, Charlottesville, Va.

Elevation of bodily temperature frequently precipitates recurrent herpes simplex infections, which suggests that temperature has an important effect on the host-herpes virus relationship. HeLa and Au cultures were infected with herpes simplex virus and incubated for three days at four different temperatures. The cultures were observed for cytopathogenesis and titrated for virus content by the plaque count method. Little or no (0 to 136 infectious units per ml.) virus was produced in cultures incubated at room temperature (20.5 to 27.7°C.). Greater amounts of virus were produced at 30°C. (8 to 44,000 infectious units) and at 40°C. (28 to 42,000 infectious units) and the greatest amount of virus was produced at 35°C. (11,700 to 503,000 infectious units). Herpes infected HeLa cultures incubated at room temperature, which showed little or no evidence of virus production, promptly produced increased amounts of virus when the temperature of incubation was raised to 35°C. Incubation of herpes virus in media containing no cells for three days at 40°C. resulted in complete loss of virus. A small amount of virus survived incubation at 35°C., a greater amount survived at 30°C., and still more virus survived incubation at room temperature. These data indicate that temperature has an important effect upon herpes simplex infections in tissue culture.

COLONY COUNTS OF NASAL SWABS FOR COAGULASE POSITIVE STAPHYLOCOCCI. *Arthur C. White, Margaret P. Martin and Vernon Knight.** Dept. of Medicine and Dept. of Preventive Medicine, Vanderbilt Univ. School of Medicine, Nashville, Tenn.

Important problems associated with antimicrobial drugs and dissemination of drug-resistant staphylococci have long been hindered by unsatisfactory methods for quantitating the staphylococcal carrier state. In this laboratory a method has been devised for making colony counts of nasal swabs for coagulase-positive staphylococci. It involves shaking inoculated swabs in a Kahn shaker immersed in a measured volume of sterile broth, and subsequently making colony counts of dilutions of the broth. Highly reproducible results have been obtained with tests of aliquots of the original broth. In an approximately ten-week continuous study of nasal swabs from twenty-five mentally ill patients, colony counts have ranged from less than 3,000 per swab (the lowest number of colonies measurable by this procedure) to as high as 1,000,000 colonies per swab. About 55 per cent of the subjects were carriers of coagulase-positive staphylococci at any one time. A small but definite group was persistently negative throughout several weeks of observation. Individual variation was considerable but it was possible to classify most subjects as persistent and heavy

carriers, intermittent and moderately heavy carriers, or non-carriers. It is technically difficult to estimate the frequency of staphylococcal colonies under 3,000 per swab because of interfering growth of other microorganisms. This technic allows the identification of "heavy" carriers who are presumed to be the greatest hazard on hospital wards, and for that reason promises to be useful in studies of dissemination of drug-resistant staphylococci.

A DIRECT EFFECT OF PURIFIED ACTH ON DEPOT FAT IN THE MOUSE. *J. Earle White and Frank L. Engel.** Dept. of Medicine and Physiology, Division of Endocrinology, Duke Univ., Durham, N. C.

Oxycel and peptide ACTH and growth hormone (STH) induce the following metabolic changes in intact and adrenalectomized animals: fatty liver, ketosis, increase in adipose tissue and cardiac glycogen, hypoglycemia and improved glucose tolerance, and decreased urea formation from infused amino acids in nephrectomized rats. These actions are not due to mutual contamination. The influence of oxycel ACTH and STH on fat metabolism was further investigated by estimating the change in fat content of testicular fat pads of eighteen-hour fasted mice over a six-hour period. Using one fat pad as the control, the fat content of the second was decreased as follows: No treatment, -4.3 ± 1.95 per cent (S.E.), 0.1 mg. ACTH, -20.8 ± 4.80 per cent ($p < .01$), 0.5 mg. STH, -15.3 ± 2.48 per cent ($p < .01$), and 1.0 mg. cortisol, -4.1 ± 2.34 per cent (N.S.) in intact mice. In mice adrenalectomized prior to removing the first fat pad and maintained with 0.1 mg. cortisol hemisuccinate fat loss was: control, -2.6 ± 1.47 per cent, 0.1 mg. ACTH, -9.6 ± 2.06 per cent ($p < .02$). ACTH induced a significant increase in liver fat in the adrenalectomized mice. These data demonstrate another direct action of oxycel ACTH and STH on adipose tissue, and support the suggestion that mobilization of fat from depots is a true adipokinetic effect of these hormones.

CORRELATION OF THE DEGREE OF PULMONARY DISABILITY AND THE MOST COMMONLY USED PULMONARY FUNCTION TEST IN NORMAL PERSONS AND IN 1,000 PATIENTS WITH PRIMARY AND SECONDARY PULMONARY DISEASE. *Russell H. Wilson** and *Russell L. Horn.* Univ. of Texas Southwestern Medical School, V. A. Hospital, Dallas, Texas.

Many of the recently devised pulmonary function tests yield identical and duplicate information. We have performed pulmonary function tests on 1,000 patients and 100 normal persons. The patients were classified into I, II, III, IV and V categories according to severity of their respiratory disability. Normal persons were classified as 0. The MBC has been done at 30, 20, 15 and 12 seconds, and the TEC at 0.5, 0.75, 1.0, 2.0 and 3.0 seconds. The results are summarized in table form.

TABLE 1

PULMONARY FUNCTION TESTS; CORRELATION COEFFICIENTS

0.5 sec. TEC* with MBC†	$r = 0.9091$
1.0 sec. TEC with MBC	$r = 0.8873$
2.0 sec. TEC with MBC	$r = 0.6928$
3.0 sec. TEC with MBC	$r = 0.8500$
0.5 sec. TEC with 0.75 sec. EC	$r = 0.9742$
0.5 sec. TEC with degree of CPD‡	$r = 0.8715$
1.0 sec. TEC with degree of CPD	$r = 0.7707$
2.0 sec. TEC with degree of CPD	$r = 0.7213$
3.0 sec. TEC with degree of CPD	$r = 0.7059$
MBC with degree of CPD	$r = 0.8349$

* TEC = timed expiratory capacity.
† MBC = maximum breathing capacity.
‡ CPD = clinical pulmonary disability.

PHYSIOLOGY OF PULMONARY DIFFUSION IN NORMAL PERSONS AND IN PATIENTS WITH PRIMARY AND SECONDARY PULMONARY DISEASE. *Russell H. Wilson** *and Bruce E. Jay.* Univ. of Texas Southwestern Medical School, V. A. Hospital, Dallas, Texas.

Marie Krogh and others have shown that the pulmonary diffusing capacity depends on a number of physical and functional properties: (1) Uniformity of pulmonary ventilation, (2) physical properties of alveolar epithelium and capillaries, (3) rate at which the CO diffuses into (k_1) and combines with hemoglobin (k_2) in the red corpuscles, (4) velocity and volume of blood perfusing alveolar capillaries. The purpose of this study was to delineate more clearly these parameters in normal persons and in patients with pulmonary disease. Physiologic dead space was measured in twenty-one normal persons, fifteen cardiac patients and in twenty patients with pulmonary emphysema. Pulmonary diffusion capacities were measured by the method of Marie Krogh with the Forester modification. The method of Roughton and Forester was used to calculate pulmonary membrane diffusion and the pulmonary capillary blood volume.

The magnitude of the physiologic dead space used as an index of efficiency of pulmonary alveolar perfusion correlated inversely, $r = 0.7317$ $P < 0.01$, with the magnitude of pulmonary diffusion (D_L) and capillary blood volume (V_c). In presurgical patients with mitral stenosis D_L was 26.9 and 30.2 three to six months after surgery $P < 0.01$. Pulmonary capillary volume (V_c) decreased and the membrane component (D_M) increased following commissurotomy. The correlation coefficient between physiologic dead space and degree of pulmonary disability was 0.5300 $P < 0.02 > 0.01$.

CEREBRAL ELECTRICAL ACTIVITY IN ACUTE AND CHRONIC HYPERCAPNIA AND HYPOXIA. *W. P. Wilson and H. O. Sieker.** Dept. of Psychiatry and Medicine, Duke Univ. School of Medicine, and the V. A. Hospital, Durham, N. C.

The role of hypoxia and hypercapnia in altering cerebral function and electrophysiology is well recognized clinically. To elucidate the mechanisms involved, changes in the electroencephalogram were correlated with arterial blood gases, electrolytes, and glucose in subjects with acute and chronic hypercapnia and hypoxia. Studies were carried out in eighteen normal subjects and fifteen patients with chronic lung disease.

Normal subjects breathing 10 per cent carbon dioxide in air showed changes in the electroencephalogram from a normal pattern to low voltage fast or slow waves after eight minutes with the blood pCO_2 over 70 mm. Hg. A significant alteration in serum potassium was also observed. A similar study in normal subjects after a glucose load demonstrated electroencephalographic changes after two to three minutes of 10 per cent carbon dioxide inhalation. There was no significant increase in serum potassium. All the patients with chronic lung disease and hypercapnia had significant elevation of the serum potassium and only half of the group had abnormal electroencephalograms even though the blood pCO_2 exceeded 70 mm. Hg. Acute hypoxemia inconsistently altered the electroencephalogram whether hypocapnia was present or not. These data suggest the relationship of potassium to the compensatory mechanisms which maintain normal electrical activity of the brain in the face of altered blood carbon dioxide.

EFFECT OF DILUTIONAL HYPONATREMIA ON BONE SODIUM. *Robert W. Winters, Robert T. Whitlock and Louis G. Welt.** Dept. of Medicine and Pediatrics, Univ. of North Carolina School of Medicine, Chapel Hill, N. C.

Previous studies have established that changes in extracellular acid-base equilibrium and salt depletion are associated with changes in bone sodium. It has been suggested that hyponatremia may also condition the movement of bone sodium. This hypothesis was examined in the present study. Three groups of fasting adult male rats received water loads by gavage at hourly intervals for twenty-four hours according to the following plan: group I, to maintain initial body weight constant; groups II and III, to provide a sustained increase of 5 per cent and 15 per cent of initial body weight, respectively. All rats received vasopressin in oil at zero and at twelve hours. In rats of groups II and III profound hyponatremia developed (112 ± 10.4 and 98 ± 4.7 mEq./L., respectively) compared to group I (138 ± 8.1 mEq./L.). However, there were no significant changes in the bone sodium values among the three groups (I, 261.6 ± 11.3; II, 253.6 ± 6.1; III, 259 ± 7.2 mEq./kg. fat-free dry bone). These studies demonstrate that despite the induction of a larger concentration gradient for sodium between bone and extracellular fluid no movement of sodium occurred.

STEROID METABOLISM IN INFANTS: EFFECT OF SURGERY ON PLASMA 17-21 HYDROXYCORTICOSTEROID LEVELS. *Jesse L. Wofford, James D. Hardy** *and Lois P. Sampson.* Dept. of Surgery and Univ. Hospital, Univ. of Mississippi Medical Center, Jackson, Miss.

Adrenocortical function in infants following surgery has not often been studied because of the technical difficulties involved. The purpose of the present study was to examine this problem by means of serial plasma 17-21 hydroxycorticosteroid measurements, using a micromethod which permits steroid analyses using only a few cc. of plasma. The results of analyses of free and conjugated corticosteroids in eleven infants and children are shown in table on page 138.

It is of particular interest to note both the very low values for conjugates, and the low control corticoid values. These findings are at considerable variance with those in adults. However, they are in agreement with measurements we have made of plasma corticoid levels in umbilical cord blood obtained at delivery. The data support previous reports that adrenocortical activity in infants is increased by major surgery.

Age	Preoperative		4 hr. Free	Postoperative Conjugated	24 hr.	
	Free	Conjugated			Free	Conjugated
7 wk.	0.5	0.5	1.0	0.75	1.1	0.75
20 mo.	5.0	1.75	4.3	1.5	5.0	1.75
4 mo.	0.5	1.5	8.5	4.3	0.5	1.5
14 hr.	1.0	0.75	2.25	2.25	.90	1.25
5 wk.	1.5	1.0	5.0	2.3	1.64	1.25
1 mo.	2.33	0	8.2	1.0	0.5	0.0
3 mo.	5.9	1.33	7.5	3.33	6.1	.83
5 wk.	7.5	7.1	12.5	10.0	8.0	5.0
1 mo.	2.1	0.0	3.7	0.2	1.3	0.0
10 mo.	2.2	0.1	4.0	2.8	1.8	0.0
1 mo.	1.5	0.0	2.0	0.0	....	....

HEMATOLOGIC EFFECTS OF FOLIC ACID AND ASCORBIC ACID DEFICIENCY IN THE MONKEY. *C. W. Woodruff,* J. E. Dutra de Oliveia, K. P. Misra and W. J. Darby.** Division of Nutrition and the Dept. of Pediatrics, Medicine and Biochemistry, Vanderbilt Univ. School of Medicine, Nashville, Tenn.

In order to study in the monkey the hematologic effects of a deficiency of ascorbic acid (AA) and/or folic acid (PGA), fourteen rhesus monkeys were fed a purified diet (*J. Nutrition*, 59: 515, 1956). The complete diet has proved adequate for growth, pregnancy and lactation in this species. Three animals deprived of AA exhibited typical scurvy and died after 114 days with severe normocytic hypochromic anemia, normoblastic marrow, and lymphopenia. Four animals deprived of PGA died with an average survival time of 152 days. A moderate normocytic normochromic anemia was present in two, and macrocytosis in one; the marrow was consistently megaloblastic. Severe lymphopenia occurred, but was not as great as in the scorbutic animals. Four monkeys deficient in both vitamins died after 114 days with an absolute lymphopenia and granulocytopenia. A severe hypochromic anemia occurred with macrocytosis in two of these animals and the bone marrow was megaloblastic in three monkeys with erythrocyte counts below 3.0 million per cu. mm. Blood and tissue levels of these and related factors have been determined. The quantitative relationships between AA and PGA have been further explored on diets containing varying suboptimal amounts of both vitamins. Both nutrients are essential for normal hematopoiesis. Ascorbic acid "spares" PGA but PGA has no such demonstrable "sparing" effect on AA.

THE DUODENAL INHIBITOR MECHANISM IN DUODENAL ULCER PATIENTS. *Edward R. Woodward and Herbert Schapiro.* Dept. of Surgery, Univ. of California at Los Angeles, and V. A. Center, Los Angeles, Calif.

Acid in the duodenum inhibits the secretion and motility of the stomach, the "enterogastric reflex." Since a deficiency in inhibition might account in part for the excessive acid secretion characteristic of patients with duodenal ulcer the present study was undertaken. A quantitative measure of this inhibition was made in eleven patients with duodenal ulcer and in eleven normal subjects. One hundred milliliters of N/20 HCl and 50 ml. of N/100 HCl were infused directly into the duodenum and the duration of motility inhibition was measured with a transducer-recorder. With N/20 HCl the period of inhibition in normal subjects varied from ten to sixteen minutes, averaging 12.7 minutes. In patients with duodenal ulcer, inhibition lasted four and a half to twenty minutes, averaging 9.7 minutes. Using N/100 HCl the average period of inhibition in normal subjects was 4.4 minutes, and in patients with duodenal ulcer the inhibitory period was identical. Statistical analysis discloses no significant difference between normal subjects and patients with and duodenal ulcer with either test dose. It is concluded that a deficiency in the duodenal inhibitor mechanism is probably not a factor in duodenal ulcer.

FEEDBACK MECHANISMS INFLUENCING PURINE RIBOTIDE SYNTHESIS. *James B. Wyngaarden,* Harold R. Silberman and John H. Sadler.* Dept. of Medicine, Duke Univ. Medical Center, Durham, N. C.

Overproduction of urate occurs in primary gout and in certain proliferative hematopoietic disorders, although by different mechanisms. In both instances, however, excessive production of precursor nucleotides must also occur. We have investigated mechanisms regulating rates of production of purine ribotides in relatively complex pigeon liver extracts (supernatant solution from centrifugation at 105,000 × g), and have found several different feedback control mechanisms. *De novo* synthesis of inosinic acid (IMP) from glycine-1-C^{14}, formate, glutamine, aspartate, bicarbonate, ribose-5-phosphate (R5P)

and ATP is inhibited by adenine, xanthine, inosine, IMP and its higher phosphates, 5-amino-4-imidazolecarboxamide (AIC), AIC-riboside (AIC-R), and AIC-ribotide (AICRMP). When R5P is replaced by 5-phosphoribosylpyrophosphate (PRPP), xanthine and IMP are no longer inhibitory. When glycine-1-C^{14} and PRPP are replaced by glycineamide ribotide-1-C^{14} (GAR), none of these substances is inhibitory except AICRMP, whose mechanism here is probably simply dilution of an IMP precursor. The inhibitory effects of adenine and to some extent of AIC result from utilization of PRPP in forming the corresponding 5-mononucleotide. Xanthine and IMP were shown to interfere with synthesis of PRPP from R5P and ATP; AIC-R and AICRMP with GAR formation from PRPP, glutamine, glycine and ATP. IMP and especially AICRMP may be key compounds in regulating *de novo* purine synthesis.

Case Reports

Spontaneous Aneurysm of the Ductus Arteriosus*

A Review and Report of the Tenth Adult Case

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Edinburgh, Scotland

SPONTANEOUS aneurysm of the ductus arteriosus is uncommon and interpretations of the lesion have shown wide variation. The records of sixty cases have been traced. They are divisible into two distinct groups according to age at the time of death. There is an infant group of fifty-one cases [*1–32*], only one of which exceeded two months of age [*23*], and an adult group of nine cases [*21,33–39*], only one of which was less than fifteen years of age. In the infant group the aneurysm was not suspected during life and was often unrelated to the infant's death. In the adult group the aneurysm has presented as a mediastinal tumour and murmurs have usually been absent; only one of these cases has been described in full, with clinical, macroscopic and histological findings [*39*]. In both groups the ductus was usually occluded by thrombus or partially closed. Traction aneurysms of the arch of the aorta [*40,41*], minor swellings detected during operation on an otherwise typical persistent ductus arteriosus [*42*] and similar lesions listed but not described [*43*] are not considered here.

The lesion is probably less rare than the few case reports in the medical literature suggest. In the infant group individual authors have seen several examples. Thus, Thore [*5*] recorded eight cases in 1,000 autopsies; Gérard [*16*] recorded two in 200; four of five cases recorded by Birrell [*31*] occurred in approximately 1,200 autopsies over a period of four years [*44*], and Das and Chesterman [*45*] referred to three recent but unreported cases. In the adult group three of nine cases were seen by one author [*37,38*].

This paper attempts to clarify the nature, pathogenesis and interrelationship of the various types of ductus aneurysm. The clinical and pathological findings in an adult, who presented clinically as an aortic aneurysm and died as the result of rupture of an aneurysm of the ductus into the oesophagus, are reported in full. The clinical diagnosis, and the possibility of surgical treatment in the adult group, are discussed.

CASE REPORT

The patient was a fifty-eight year old woman. There had been no serious illnesses and no symptoms until five weeks before death. The first complaint was vomiting after meals. A week later pain in the chest developed and was almost constant thereafter; it radiated through to the back and down the left arm as far as the elbow. The patient became restless, had difficulty in breathing and sometimes sweated and felt sick. She became breathless on exertion and liable to paroxysmal nocturnal dyspnoea. Two weeks before death she had a haematemesis, was awakened from sleep by a particularly severe episode of pain in the chest, and was admitted to the hospital. On examination she was pale and afebrile. The cardiac rhythm was normal but her heart rate was rapid at 120 per minute; her blood pressure was 112/74 mm. Hg. There was no cardiac enlargement or abnormality of precordial pulsation. The first heart sound was widely split and there were episodes of gallop rhythm, but no murmurs. The haemoglobin was 90 per cent (Sahli); the white cell count, 10,300 per cu. mm.; the erythrocyte sedimentation rate, 102 mm. in the first hour (Westergren); and the Wassermann reaction was negative. The electrocardiogram (Fig. 1) showed widespread ST-T wave changes, but no evidence of recent infarction. Radiographs showed a soft tissue mass in the anterior mediastinum; there was extensive

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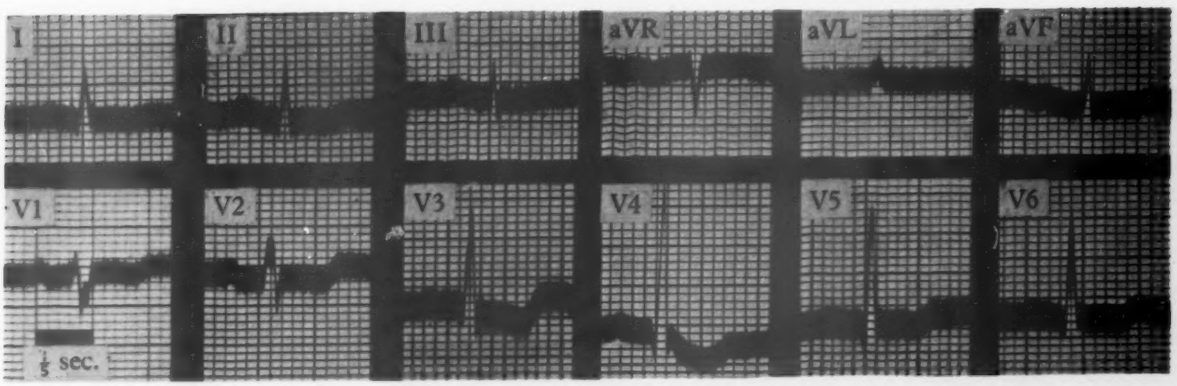
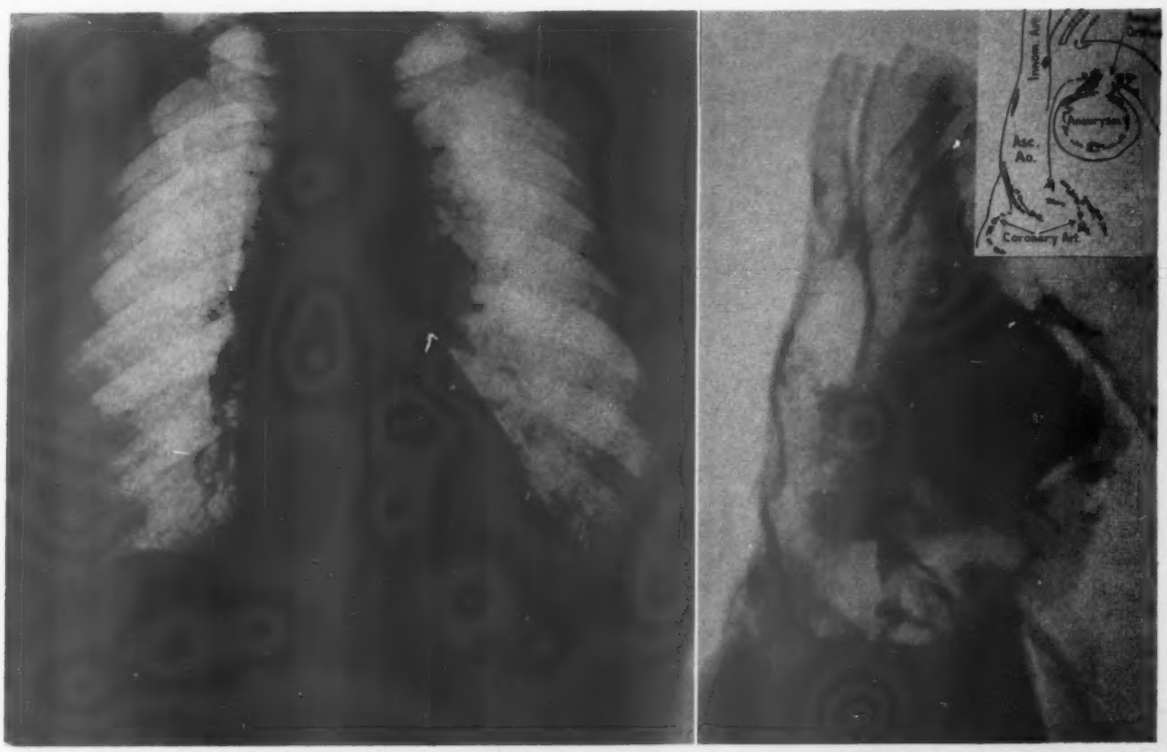


FIG. 1. Electrocardiogram, showing non-specific ST-T wave changes, in keeping with myocardial ischaemia and the myocardial fibrosis revealed postmortem.



2A 2B

FIG. 2. A, anterior radiograph, showing calcification in the aortic knob and in the aneurysm below it; displacement of the trachea and barium-filled oesophagus to the right; atelectasis and fibrosis of lung adjacent to the aneurysm. B, radiograph of the specimen, showing calcification in aneurysm, aorta and coronary arteries. The dense calcification around the aortic orifice of the ductus is well seen.

calcification in the aorta and some in the mass. (Fig. 2A.) During the subsequent two weeks she had recurrent small haemoptyses followed by haematemeses. Her haemoglobin fell and she required repeated blood transfusions. The day after admission she had a rise in temperature to 102°F. and her sputum yielded a growth of pneumococci. She responded rapidly to penicillin therapy, but the erythrocyte sedimentation rate remained over 100 mm. in the first hour. The mediastinal tumour increased in size. A soft, blowing, early, diastolic murmur became audible at the left border of the sternum and her diastolic blood pressure fell to 40 mm. Hg. Auricular fibrillation and oedema of the sacrum developed. Five weeks after the onset of symptoms, she had a large haematemesis and died five minutes later.

At autopsy, the heart was normal in size. A small patch of old standing fibrosis was present in the anterior wall of the left ventricle. Scattered small patches of fibrosis were present in the myocardium

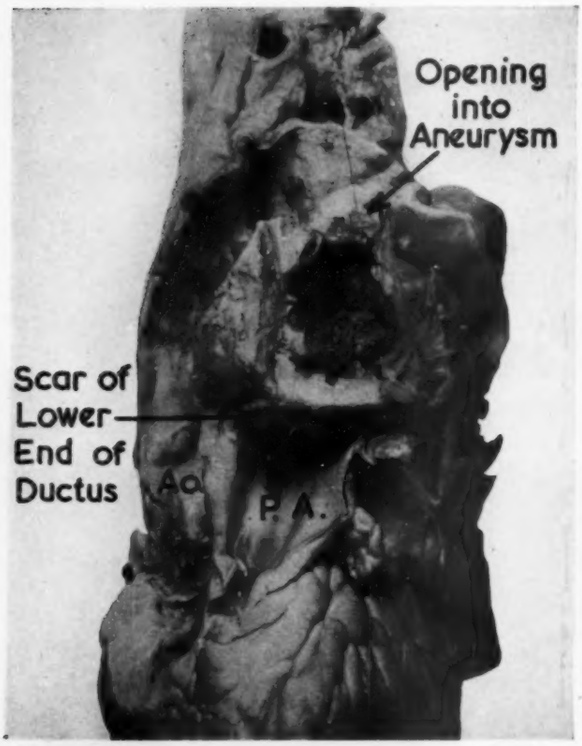


FIG. 3. Left oblique view, showing aneurysm filled with thrombus lying between arch of aorta and pulmonary artery. The black rod is in the left subclavian artery and the arrow behind the left recurrent laryngeal nerve. The scar of the lower end of the ductus is seen on the intima of the pulmonary artery, just below the aneurysm.

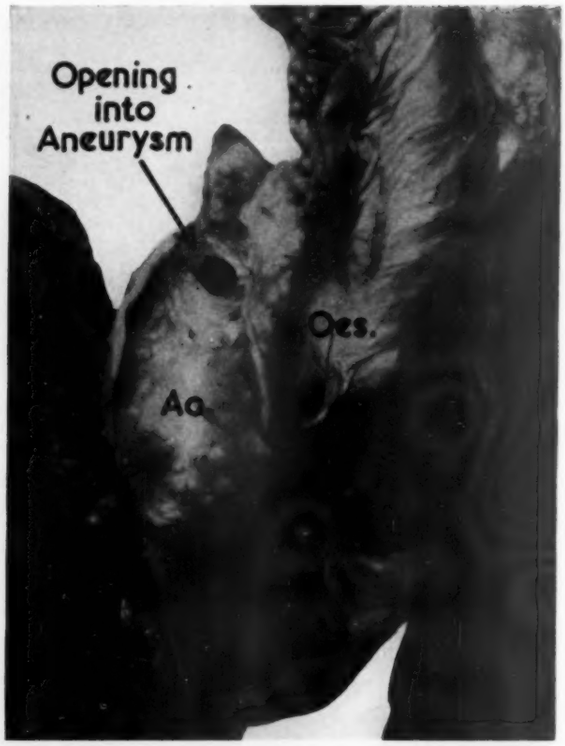


FIG. 4. Posterosuperior view, showing circular opening from aorta into aneurysm and perforation into oesophagus.

of the left ventricle, but there was no evidence of recent infarction. There was slight thickening of the chordae tendineae of the mitral valve and, in the valve itself, extensive atheroma involved mainly the medial cusp, but did not cause either stenosis or incompetence. The cusps of the aortic valve showed considerable thickening by atheroma, with fibrosis and calcification. The cusps were slightly adherent at the commisures, so that mild stenosis and incompetence were present. There were no vegetations on any valve cusp. There was generalised dilatation of the ascending aorta and extensive atheroma, with partial calcification. No evidence of syphilitic aortitis was seen, nor were there any mural thrombi. Similar atheroma was present in the arch of the aorta. The great vessels were all normal in situation and size, but showed marked atheroma. Detailed examination of the main coronary arteries was not made at autopsy, in view of the desirability of preserving the heart and great vessels. Patchy atheroma was seen in small branches in the apical portion of the heart. A radiograph of the specimen showed considerable calcification of the main coronary vessels. (Fig. 2B.) An aneurysm lay between the arch of the aorta and the pulmonary artery. (Fig. 3.) It measured 3 cm. vertically and 4 cm. in lateral and anteroposterior planes. Its aortic opening was a rounded hole, 1 cm. in diameter, situated 1 cm. distal to the orifice of the left subclavian artery and on the lower side of the arch. (Fig. 4.) Extensive calcification was present in the wall of the aorta around this hole and for some distance on all sides of it, so that a shelf of calcified tissue was present between the lumens of the aorta and the aneurysm. (Fig. 2B.) The aneurysm was adherent inferiorly to the pulmonary artery, but did not open into it. The scar at the lower end of the ductus arteriosus was seen as a brownish depression 5 mm. in diameter on the superior aspect of the intima of the pulmonary artery immediately opposite the aneurysm. (Fig. 3.) It was impossible to separate the aneurysm from the wall of the artery in this region, therefore, the ligamentum arteriosum was not identified. The right boundary of the aneurysm was in contact with the wall of the ascending aorta, and its left with the upper lobe and hilum of the left lung. Anteriorly it was bounded by a layer of calcified fibrous tissue 3 to 5 mm. thick and posteriorly by the descending aorta, the oesophagus and the left main bronchus, from each of which it was separated by another layer of calcified fibrous tissue. Perforation into the oesophagus had occurred at the level of the upper border of the bifurcation of the trachea. (Fig. 4.) The left vagus nerve was identified in the scar tissue on the anterior aspect of the aneurysm and

the left recurrent laryngeal nerve was traced from the thyroid region, down the groove between the oesophagus and the trachea into the fibrous tissue forming the left side of the wall of the aneurysm, where it became deeply embedded in this tissue. The lumen of the aneurysm contained clotted blood. In the upper lobe of the left lung a large fibrous scar was present at the site of adhesion of the aneurysm. The scar extended for several centimetres into the lobe and, on section, showed a large thrombus surrounded by a well developed fibrous capsule. Patchy intra-alveolar haemorrhage was seen, mainly in the lower lobes, where there was also mild bronchiectasis. The lower end of the oesophagus, the stomach and the first part of the duodenum were filled by a large, recent blood clot and much altered blood was found further down in the intestines. No significant abnormality was seen in any other organ.

Microscopic examination of multiple blocks taken from the aorta and from the wall of the aneurysm showed no lesion suggestive of syphilitic aortitis. In the aorta, the appearances were those of atheroma. The wall of the aneurysm consisted of non-specific granulation tissue of varying cellularity; in the inner part, remains of blood clot were found and the tissue was both cellular and vascular, whereas further out it became progressively more fibrous. Elastic tissue was present in places as irregular, thick, short, straight fragments, arranged in groups lying circumferentially and separated by collagen fibres. One block taken from the anterior wall of the aneurysm contained a large nerve trunk, which was considerably narrowed and encroached upon by the granulation tissue. A section from the lesion in the upper lobe of the left lung showed similar appearances to those in the wall of the aneurysm.

The pathological diagnosis was aneurysm of ductus arteriosus with erosion of upper lobe of left lung and perforation into oesophagus; atheroma of aorta and aortic valve; bronchiectasis.

COMMENTS

The lesion in this patient was considered to be of the ductus because of its situation, its relation to other mediastinal structures and the character of its aortic orifice. Despite this apparently simple explanation, the lesion is complex. Any attempt to elucidate its nature and pathogenesis necessitates a review of other forms of ductus aneurysm and a comparison of such features as they have in common.

Nature of the Lesion. The usual lesion in infants has been a round or fusiform swelling of the ductus, situated nearer its aortic than its pulmonary arterial end. It was sometimes associated with dissection and rupture of its wall [*10,11,13,14,23,24,31*] and was occluded by clotted blood in twenty-seven cases. The interpretation of this lesion as an aneurysm has been doubted [*17,46–48*]. These authors believed that the swelling represents simple distention of the ductus to its full capacity by clotted blood. Rokitansky [*46*] considered swelling of the ductus insignificant and obliteration by blood clot its normal method of closure. Gérard [*16*] also suggested that organisation of clot converts the dilated ductus into the normal ligamentum arteriosum and several recent writers have been of the same opinion [*27,30,31*]. The fact that death was unrelated to the vascular anomaly in twenty-three of the fifty-one cases would be in keeping with this interpretation. Nevertheless, there are strong arguments for regarding the lesion as a true aneurysm of the ductus. The size of some of the swellings [*4,5,16,20,27,28,30,31*] has been greater than the diameter of the normal ductus at this age. Moreover, extensive histological studies of the normal ductus have demonstrated that thrombosis is a rare method of closure [*25,49*], whereas it was present in twenty-eight of these infants. Necrosis of the wall was present in four of the twelve instances in which histological appearances have been recorded [*27,30,31*]. Necrosis [*49*], ischaemic degeneration [*50*] and mucoid degeneration [*25,51*] have been described in the apparently normal ductus, but such changes are well recognised as leading to localised dilatation of other vessels and are likely to be the cause of aneurysm of the ductus in the infant.

The rarity of the lesion in older children and adults and the incomplete nature of most of the reports makes it difficult to obtain a clear picture of the condition after infancy. However, most of the recorded cases can be regarded as having in common a basic lesion, upon which further changes may be superimposed. This basic lesion must be regarded as an aneurysm of the ductus arteriosus, or of that portion of the vessel which has remained patent, for the following reasons: it communicates with the aorta at the site of the ductus; the pulmonary orifice is usually closed and a portion of the lower end of the ligamentum arteriosum may be present; the lumen may contain fluid or clotted blood and the walls consist of vascular or calcified connective tissue; the lesion may erode the left lung or the vertebral column. The case recorded by Mönckeberg [*21*], Graham's first case [*37*] and Dvorak and Schmittova's case [*39*] fulfilled all or most of these criteria; Graham's second case

[*37*] and that of Mackler and Graham [*38*] were probably similar. The case reported in this paper fulfills all the criteria of this lesion. In addition the left recurrent laryngeal nerve was identified in its wall and its aortic orifice was surrounded by extensive calcification similar to that which occurs in those examples of persistent ductus in older patients seen at autopsy [*52,53*]. The lesion had eroded the left lung and the oesophagus. The basic pattern may have been similar in three more of the recorded cases, but with associated stenosis of the pulmonary arterial tree [*33*], superimposed dissecting aneurysm [*35*], and superimposed mycotic aneurysm [*36*].

Pathogenesis. Aneurysm of the ductus arteriosus in infants is probably related to the structural changes in the wall of the ductus subsequent to its functional closure. Barclay, Franklin and Prichard [*54*] have demonstrated that functional closure of the ductus precedes its anatomical obliteration, and an aneurysm of the ductus has not been described in a stillborn infant. The frequent presence of thrombus suggests that there was no free circulation through the vessel immediately before death; indeed, the vessel was recorded as patent in only twelve cases. The presence of thrombus may be due to continuing patency at the aortic end after closure of the pulmonary arterial end; this was the anatomical situation in three cases [*23,24,31*] and the aortic end was considerably larger than the pulmonary arterial end in another five cases [*16,20,27,28,31*]. In a ductus in which the aortic end remains patent after the pulmonary artery end has closed, the naturally thin, and by this time degenerate, wall of the ductus is exposed to the force of the aortic blood stream until thrombosis occurs, so that dilatation is all the more likely to be found in these circumstances. It is difficult to assess the role of sepsis in initiating aneurysm formation in infants. The findings are compatible with such a cause in the case recorded by Lennox and MacCarthy [*30*], and Scheef [*24*] thought that the infection introduced at paracentesis in his case was responsible for the formation of the aneurysm.

Intramural haemorrhage as a possible factor in the pathogenesis of aneurysm of the ductus was discussed briefly by Mackler and Graham [*38*], but its significance has not been discussed by other writers, although haemorrhage has been observed in the wall of the normal ductus [*50,51,55,56*] and in aneurysms [*4,23,24,31*]. Nine dissecting aneurysms of the ductus have been described [*11,13,14,23,24,31*], in four of which death was due to rupture of the aneurysm. Intramural haemorrhage with death in infancy from rupture of an undilated ductus has also been described [*55–57*]. The association of intramural haemorrhage with dissecting aneurysm of the ductus is analagous to that which is well recognised in dissecting aneurysm of the aorta [*58,59*] and the histological changes in these two conditions are very alike. The possibility that a dissecting aneurysm of the ductus may persist beyond the first two months of life is suggested by the observation of four examples of this lesion in infants in whom death appears to have been unrelated to the vascular anomaly [*25*]. It is conceivable that, if these infants had lived, the lesion in the ductus might have presented as a mediastinal tumour later in life. This suggestion is supported by the length of survival of patients with dissecting aneurysm of the aorta for three to six years [*60*] and of cases of surgical aneurysms of the ductus for eight years [*61*].

Previous workers have expressed the opinion that spontaneous aneurysms of the ductus occurring in older children and adults have various origins [*30,31*] but that they are unrelated to those seen in infants [*31*]. However, the basic lesion in such cases bears so much resemblance to that described in infants that it is likely that the pathogenesis of the two groups is related. Indeed, Lennox and MacCarthy [*30*] interpreted Hutchison's case [*35*] as persistence of an aneurysm which arose in infancy.

Persistence of the infant lesion does not appear to be the main cause of spontaneous aneurysm of the ductus in adults. Normal closure of the ductus begins at the pulmonary arterial end [*25,28,62,63*] and most persistent ductuses observed at thoracotomy have the shape of a truncated cone, the narrowest point being at the pulmonary arterial end. Arrested closure, at the stage of obliteration of the pulmonary arterial end is, therefore, another possible cause for the adult type of aneurysm. We have recently seen such a ductus in a ten year old boy. The pulmonary orifice was occluded but the rest of the vessel was in free communication with the aorta. There were no physical signs referable to the ductus, although a persistent ductus in two siblings had required surgical occlusion. Spontaneous closure of the ductus in later life has been described [*64–67*], although it is not known whether or not this follows the same sequence as normal closure. The fact that the aortic orifice was patent in all

the adult cases fully described pathologically suggests that arrested or late spontaneous closure may be the principal causes when the lesion is seen after infancy. In either event a patent portion of the ductus, remaining as an aortic cul-de-sac, would be liable to aneurysmal dilatation. Furthermore, unless occluded by thrombus, such an aneurysm would be likely to increase in size and eventually compress or erode surrounding structures in the same way as a saccular aneurysm of the aorta itself. In two of the adult cases the aneurysms were over 10 cm. in one diameter [*37*,*39*].

The role of sepsis is probably more important in the adult than in the infant. Bacterial endocarditis has led to aneurysm of a persistent ductus [*45*] and of a recanalised ductus [*68*]. Infection was probably responsible for the aneurysmal dilatation in Hammerschlag's case [*36*]. The transient paralysis of the left recurrent laryngeal nerve in a patient with bacterial endoarteritis who recovered spontaneously [*69*] may have been due to temporary dilatation of the ductus. Although the most likely result of sepsis is weakening of the wall of the ductus, spontaneous closure, with recovery from endarteritis has been recorded [*67*]. Occlusion of the pulmonary arterial end of an inflamed ductus would increase the strain on the wall of the patent portion of the vessel, so that infection might play a double role. This appears to have happened in Hutchison's patient [*35*], for the history suggested recurrent pulmonary infarcts from an infected patent ductus, as described by Gilchrist and Mercer [*70*], whereas autopsy showed occlusion of the pulmonary arterial end of the ductus, as well as a pulmonary lesion which could have resulted from an infected pulmonary infarct.

The possibility that external trauma to the chest plays a part in the formation of an aneurysm of the ductus cannot be dismissed, for traumatic aneurysm of the aorta is well recognised. Two cases of aneurysm of the ductus in adults have been involved in motor accidents [*37*,*38*], and Dvorak and Schmittova [*39*] discussed the possibility that the boxing indulged in by their patient might have been an aetiological factor.

In the case reported in this paper, the absence of an impingement plaque in the pulmonary artery suggests that closure of this end of the ductus occurred early in life. The pathogenesis is therefore likely to have been either persistence of an infant type of aneurysm or arrested closure at the stage of obliteration of the pulmonary arterial end. In either event the aortic orifice has remained patent and subsequent development has followed the usual pattern of the aneurysm of the aorta. The wall of the ductus has become replaced by fibrous tissue which has gradually given way under the pressure of aortic blood. There has been intraluminal clotting with the gradual formation of laminated clot on the inner surface of its wall. Calcification has replaced some of the fibrous tissue. There was nothing definite to suggest intramural haemorrhage, dissection or slow leakage from the aneurysm, nor was there evidence of past infection or trauma, but none of these factors can be excluded on the basis of the information available.

Clinical Features. In the infant cases the clinical features which have been recognized and recorded have seldom been sufficient to direct attention to the aneurysm, even when rupture or embolism has been the cause of death. Traum [*71*] reported the clinical features in Guggenheim's case [*23*] and mentioned that the child was hoarse. Murmurs were usually absent. Radiological examination may be of no assistance in infants [*71*], but serial radiographs showed the development of a soft tissue swelling in the region of the ductus in Scheef's case [*24*]. Kneidel [*28*] has also suggested that radiography may be of value in the recognition of aneurysms of the ductus in infants.

More information is available in children and adults, but the scope of any account of the clinical features is limited by the small number of recorded cases, by the scanty records of clinical details and by the superimposed complications in some of them. Two patients presented with signs of septicaemia which dominated the clinical picture [*35*,*36*]; in another the clinical picture was obscured by pulmonary tuberculosis [*33*]; there was no pathological confirmation of the nature of the lesion in Graham's second [*37*] or third [*38*] cases; in Thorel's case [*34*] there was rupture into the pericardium, leading to death at fifteen years of age, but neither clinical nor pathological details were given. The two patients with septicaemia have clinical implications, for aneurysm of the ductus should be considered in the differential diagnosis of the more common aneurysm of the pulmonary artery complicating bacterial endarteritis of a persistent ductus. This consideration is especially important if the continuous murmur disappears.

There are only two confirmed and uncomplicated cases [*37,39*], in addition to our own, from which to draw firm conclusions. Cough and dyspnoea were present for about six years in the absence of infection in Graham's case [*37*], cough was a late feature in the case of Dvorak and Schmittova [*39*] and breathlessness was a late symptom in our case. A dry, hacking cough has also been reported in traction aneurysm of the arch of the aorta [*72*]. Haemoptysis may occur during the last few weeks [*37,39*] and this feature is shared by some of the examples of false aneurysm occurring after surgical treatment of persistent ductus [*61,73,74*]. It is usually due to erosion of adjacent lung tissue in both conditions. There may be hoarseness, due to recurrent laryngeal paralysis, anorexia and loss of weight [*21,39*]. Severe pain dominated the clinical picture in the case of Dvorak and Schmittova [*39*] and in our own case, in which its nature suggested myocardial infarction or dissecting aneurysm of the aorta. This latter diagnosis was supported by the late detection of an early diastolic murmur at the left edge of the sternum [*75*]. The heart sounds are usually closed. A continuous murmur and other evidence of persistence of the ductus have been present in only one case [*39*]. The initial period of vomiting in our case may have been due to irritation of the oesophagus.

None of these clinical features is diagnostic, but any combination of cough, haemoptysis, dyspnoea and pain in the chest indicates the need for radiological examination, upon which a suggestion of the clinical diagnosis of aneurysm of the ductus is almost exclusively based [*38*]. The aneurysm is evident radiologically as a mediastinal tumour in the region of the main pulmonary artery. It may lie posterior [*38*] or anterior to the trachea, as in our case, and it usually displaces the trachea to the right [*39*]. An anterior position of the aneurysm has also been detected in the infant [*28*]. Expansile pulsation of the lesion may, or may not, be present and is not necessary for the diagnosis [*38,39*]. A rim of calcification in the periphery of the lesion is characteristic, but postoperative cases demonstrate that this may take a year or two to develop [*61*]. If calcification is present, this may raise the question of an aneurysm, but similar appearances may be caused by any dissecting aneurysm in this region, whether spontaneous or traumatic [*76,77*]. Location of the aneurysm posterior to the trachea has been taken as suggestive of aneurysm of the ductus [*38*] but the appearances are not diagnostic. The lung adjacent to the aneurysm may show radiological signs of consolidation due to compression, fibrosis or haemorrhage. This was a striking feature in our own case; in postoperative cases the same type of radiological appearance has been seen [*61*], and may vary with incidents of haemoptysis [*73*]. Angiocardiography may aid the diagnosis [*39*], as it may in dissecting aneurysm of the aorta [*78*]. Cardiac catheterisation was attempted by Dvorak and Schmittova [*39*], but, even when the ductus is patent throughout its course, this procedure is probably unwise in view of the frequency with which the aneurysm contains thrombus. When pain is severe electrocardiography may be of value in excluding recent myocardial infarction.

Prognosis and Treatment. Most aneurysms recorded in infants were detected as an incidental finding at autopsy. It seems likely, therefore, that many of these lesions undergo thrombosis and obliteration. Nevertheless, death was due to rupture in five cases [*10,11,23,24,31*] and to embolism in another three [*26,28,29*]. No patient in this group has been treated surgically.

The prognosis in children and adults is probably not as bad as the case reports suggest, but the occurrence of spontaneous rupture in two of the nine previous cases [*34,35*] and in our own case, and the known fate of aortic aneurysms cannot be ignored. The severity of symptoms and signs may raise the question of surgical treatment. This has been attempted on four occasions, but in all these patients the lesion was large, and operation was found impracticable [*37,38*] or ended in fatal haemorrhage [*37,39*]. Recognition of aneurysm of the ductus as one of the causes of mediastinal tumour, diagnosis while the lesion is still relatively small and not adherent to surrounding structures, an appreciation of its nature and advancing experience in aortic surgery [*77,79*] should overcome most of the difficulties in the future. Surgical treatment has proved successful in the repair of the false aneurysms which sometimes develop after the operative occlusion of a persistent ductus [*45,61,73,74,80,81*]. The surgical problem of the spontaneous aneurysm is essentially similar. The main risk is bleeding and readiness to control sudden haemorrhage has been shown to be the most important consideration [*61*]. An attempt at surgical treatment would probably have been justified in our patient, but her age, the close attachment to the oesophagus and the advanced

atheroma of aorta and coronary arteries would have increased the risks and might have prevented satisfactory aortic repair.

CONCLUSIONS

Available evidence suggests that aneurysm of the ductus arteriosus in infancy results from a fault in the normal anatomical closure of the ductus. In older children and adults the pathogenesis is probably more complex and there appear to be one or more of four possible explanations:

1. Persistence of an infant type of aneurysm into later life,
2. Arrested closure of the ductus at the stage of obliteration of its pulmonary arterial end,
3. Late spontaneous closure of the pulmonary arterial end with, or without, superimposed bacterial endarteritis and
4. External trauma to the chest of a patient with persistence of the whole or part of the ductus.

The primary abnormality in each circumstance is a fault in the closure of the ductus. This links spontaneous aneurysms with those which sometimes develop after operative occlusion of a persistent ductus. There are, thus, three distinct, but related, forms of ductus aneurysm—the infant type, the adult type and the surgical type.

All forms of ductus aneurysm are liable to rupture. The infant type may present clinically with an embolic episode; the adult type with cough, dyspnoea, haemoptysis and pain in the chest. The characteristic clinical features of persistence of the ductus are usually absent. The differential diagnosis is from other forms of mediastinal tumour.

Operative repair has been successful in the surgical type. It should prove possible in some of the adult type. The difficulty of diagnosis has so far prevented the infant type from presenting as a surgical problem.

SUMMARY

1. The clinical, radiological and pathological features are reported in a patient who survived until the age of fifty-eight years and died from rupture of a spontaneous aneurysm of the ductus arteriosus into the oesophagus.

2. This case is analysed in conjunction with the findings in the sixty recorded cases of spontaneous aneurysm of the ductus. These cases are divisible into an infant group of fifty-one cases and an adult group of nine cases.

3. The nature and pathogenesis of the aneurysm are basically similar in the two groups, arising as a fault in the closure of the ductus.

4. The infant lesion is usually an incidental finding, unrelated to the infant's death; the adult lesion usually presents as a mediastinal tumour. The clinical features of the latter are discussed.

5. Some aneurysms of the adult type should be amenable to surgical treatment.

Acknowledgments: We are grateful to Dr. A. Rae Gilchrist for permission to quote the clinical records of his patient and to Mr. L. Jolley, formerly Librarian to the Royal College of Physicians of Edinburgh, for much help in tracing references.

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Adult Agammaglobulinemia Associated with Multiple Congenital Anomalies*

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IN 1945 a twenty-five year old white married male truck driver was medically discharged from the Army because of chronic iritis. In 1949 he was hospitalized twice at Winter Veterans Administration Hospital with chronic conjunctivitis and once with acute cellulitis of the hand. In 1950 he was again hospitalized with chronic bronchitis. There followed a series of abscesses of the skin, which finally subsided after vaccine therapy in 1951. In 1954 he was hospitalized with severe acute pneumococcic meningitis. Shortly after recovery from the meningitis chronic diarrhea developed, there was weight loss and fatigue, and the patient was forced to cease work. After nine months of continuing diarrhea he reentered the hospital in 1955 at the age of thirty-five years.

His past history revealed only the usual illnesses of childhood, and a tonsillectomy. He had smoked cigarettes but had used no alcohol or drugs. His wife and child, and both parents, were not unusually susceptible to infections. There were no siblings.

The patient's child was not available to us but the blood of both parents were examined. The father's blood group was O, Rh negative and D^u negative, and contained normal amounts of isohemagglutinins a and b. The mother's blood group was A, Rh positive, and contained normal amounts of isohemagglutinin b. Both parents had high serum gamma globulin turbidity levels, the father's being 2.11 gm. per cent and the mother's 1.69 gm. per cent. By paper electrophoresis, the father's gamma globulin fraction was 21.2 per cent, the mother's 16.8 per cent.

The patient presented an asthenic physique, was 70 inches tall and weighed 138 pounds; he appeared chronically ill. The brow was unusually prominent. (Fig. 1.) Mild hyperopia was present, and exotropia for both distant and near vision. An area of pigmented and hyalin degeneration of the retina was found adjacent to the left optic disc, and there was some enlargement of the blind spot of the left visual field. Many purulent gingival infections were present.

A slight dorsal scoliosis was noted. There was a slight respiratory lag of the left side of the chest, and moist rales were found in the lower left axillary area. The pulse was regular at a rate of 68 per minute. The blood pressure was 105 mm. Hg systolic and 60 mm. Hg diastolic. Abdominal organs were not recognizable by palpation. A ring of internal hemorrhoids was found, and an area of granularity of the rectal mucosa.

A large irregular bony mass in the upper left arm proved on roentgenographic examination to be an osteochondroma. (Fig. 2.) The fingers and toes were clubbed. There were scattered scars of old healed abscesses over the entire body, many dozens in number. On the legs were approximately a dozen erythematous indurated areas up to 6 cm. in diameter, with purulent crusting. A moist, reddened and peeling periungual mycotic lesion was present on the right great toe. Prominent lymph nodes were found in all accessible areas.

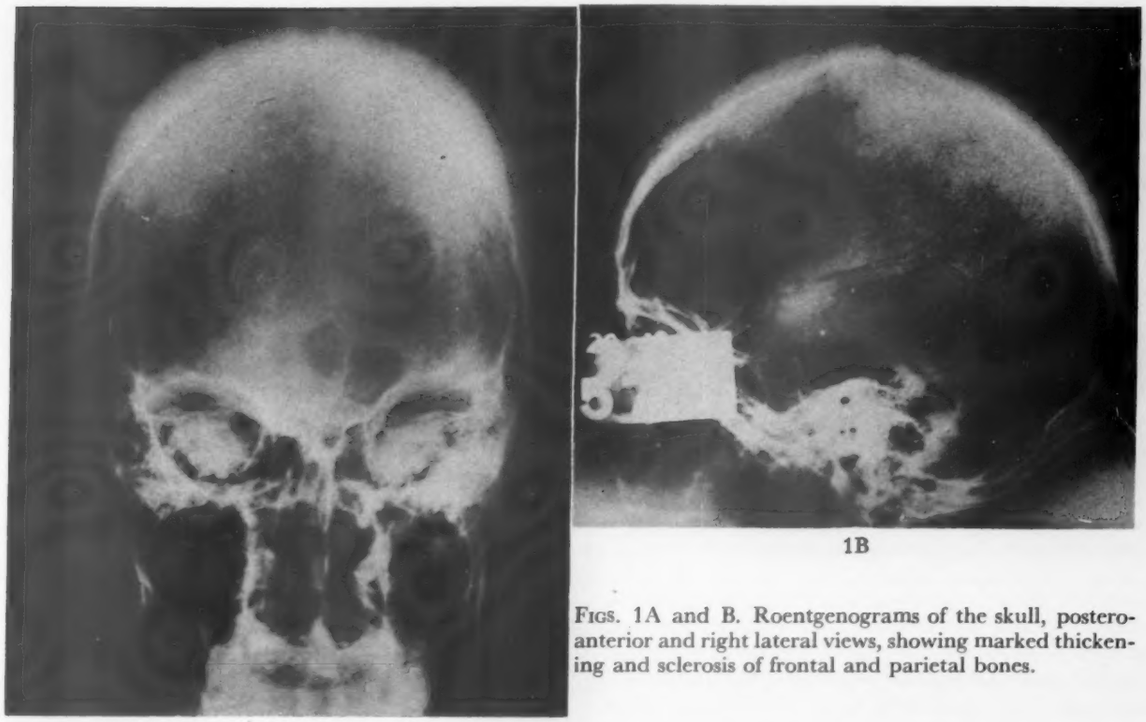
Electroencephalograms taken while the patient was asleep and awake revealed no abnormalities. Roentgenograms of the chest revealed peribronchial infiltrations in both lung fields. (Fig. 3.) X-ray films of both hands failed to show the cystic lesions of sarcoid, but confirmed the clubbing noted on physical examination.

Sigmoidoscopic examination revealed an erythematous and granular, tender friable mucosa of the rectum and lower sigmoid, with patchy rectal but diffuse sigmoid involvement. Swabs of the sigmoid colon contained erythrocytes and granulocytes but no amebae, and stool cultures revealed no pathogens. Irritability of the descending colon was found on fluoroscopic study. Because the hepatic flexure of the colon was depressed, intravenous pyelographic and cholecystographic studies were performed, revealing a low position of the right kidney and a gallbladder which was displaced medially to the midline, with a dilated and elongated common bile duct.

Roentgenographic studies of the small bowel showed abnormalities of the barium pattern. (Fig. 4C.) An oral dextrose tolerance test yielded a flat curve (fasting 60 mg. per cent; at thirty minutes, 114; at one hour, 75; at two hours, 54; at three hours, 63). Free fat globules and soaps were found in the stools. A twenty-four-hour stool while the patient received an appropriate diet contained 1.36 gm. total nitrogen and 9.4 gm. total fat.

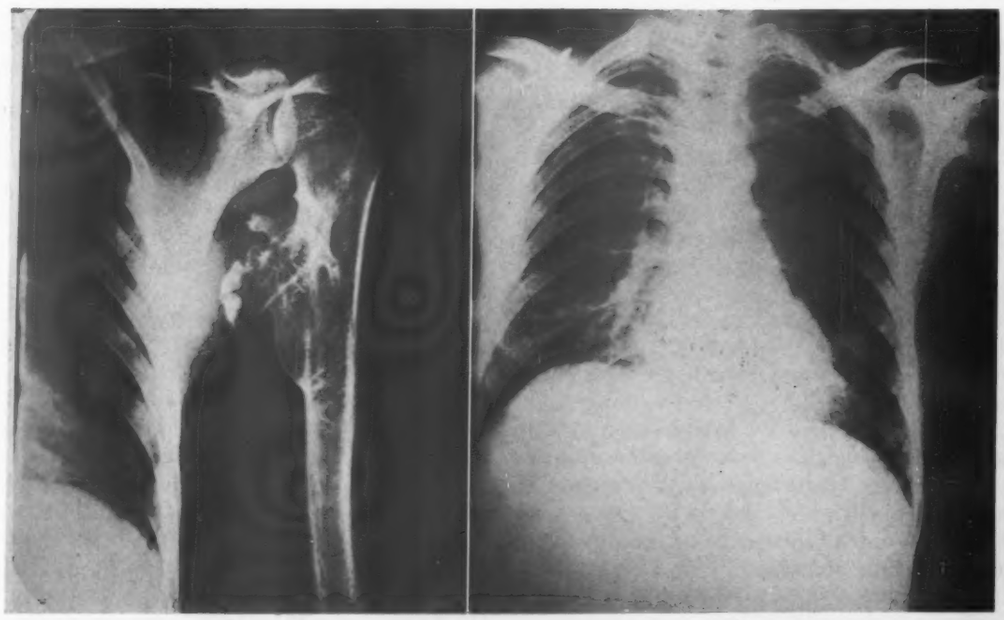
Urinalyses and routine hematologic studies were normal. The erythrocyte sedimentation rate remained at low levels. Examination for the L.E. phenomenon in the blood and bone marrow proved negative. A

*From the Winter Veterans Administration Hospital, Topeka, Kansas.



1A 1B

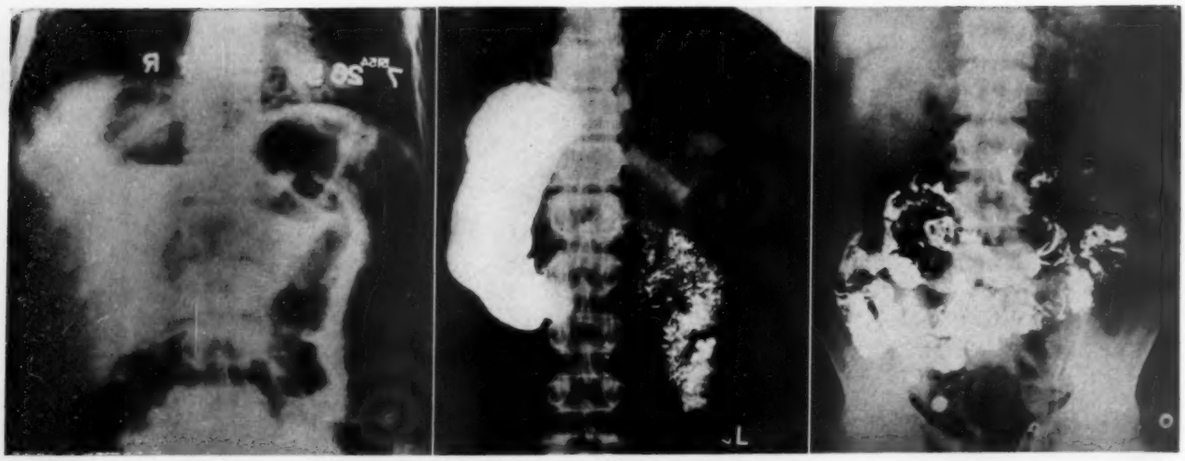
FIGS. 1A and B. Roentgenograms of the skull, posteroanterior and right lateral views, showing marked thickening and sclerosis of frontal and parietal bones.



2 3

FIG. 2. Roentgenogram of left humerus, anteroposterior view, showing a large osteochondroma.

FIG. 3. Roentgenogram of the chest, posteroanterior view, showing peribronchial infiltrations.



4A 4B 4C

FIG. 4. Roentgenograms of the abdomen, anteroposterior views. A, film taken with patient in upright position, after filling stomach and colon with gas (method of Zelman [*8*]), reveals shadows of liver, spleen, stomach, and right kidney on right side, descending colon and left kidney on left side. B and C, films taken with patient in supine position after barium meal, reveal situs inversus of lower esophagus, stomach, and duodenum, with normal position of jejunum and ileum, and sprue-like disturbance of motor function of the small bowel.

smear of sternal marrow was found to contain no plasma cells in a total of 1,000 nucleated cells counted. Sputum cultures were repeatedly positive for gram-staining cocci and Proteus organisms, but attempts to demonstrate tuberculous or mycotic organisms failed. Cultures of sternal marrow and splenic aspirate (liver aspirate intended) grew no organisms.

Agglutination of serum against typhoid H and O antigens, paratyphoid A and B, Brucella abortus, and Weil-Felix OX19 organisms yielded entirely negative results, despite a history of typhoid-paratyphoid inoculations during Army service. Heterophil antibody was absent. The C-reactive protein of the serum showed marked fluctuations, sometimes being strongly positive but more often absent. The result of a Coombs' test for incomplete antibody was negative. The patient's blood cells were typed as group O, Rh positive. His serum was typed against known A and B cells and was found to contain no isoagglutinins a and b. Tuberculin tests, histoplasmin skin test, and repeated Schick tests were all negative. The Dick test was positive.

The serum proteins showed fluctuating total globulin fractions, which varied from as high as 3.1 gm. to as low as 0.4 gm. per cent, being most often about 1 gm. per cent. The turbidity tests dependent on gamma globulin fractions were low, the serum zinc turbidity, 2 units; the thymol turbidity, 0.5 unit; and the cephalin flocculation test, negative.

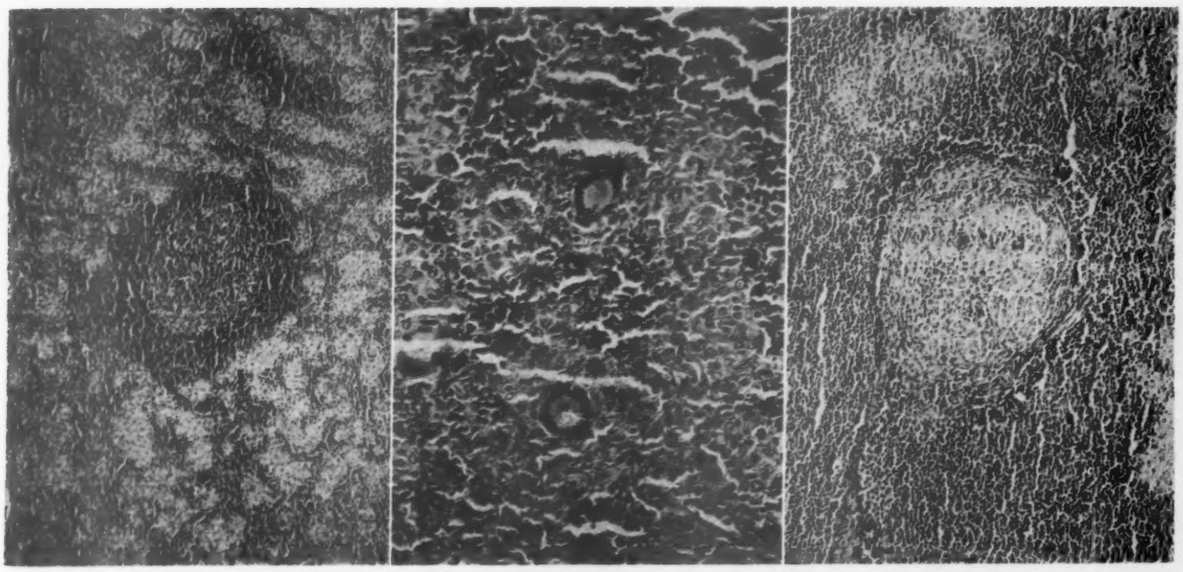
Paper electrophoretic fractionations of serum proteins were performed at the Kansas University Medical Center by Dr. Robert E. Bolinger, and repeatedly at Winter Veterans Administration Hospital by Dr. Chi Che Wang, all determinations showing near absence of the gamma globulin fraction. Fractionation of plasma revealed normal fibrinogen fraction. Further studies were carried out by Dr. William Q. Wolfson at the U. S. Army Hospital Medical Laboratory, Fort Riley, Kansas. Dr. Wolfson's figures were:

	Patient	Normal Pool
Albumin	43.3%	54.3%
Alpha globulin	33.8%	17.8%
Alpha 1	13.3%	5.8%
Alpha 2	20.5%	12.0%
Beta-globulin	18.3%	15.8%
Beta 1	12.3%	9.8%
Beta 2	6.0%	6.0%
Gamma globulin	4.6%	12.1%
Gamma 1	2.0%	4.3%
Gamma 2	2.6%	7.8%
Fast gamma 2	2.6%	6.1%
Slow gamma 2	0.0%	1.7%

Although Dr. Wolfson's study was made after initiation of monthly injections of 10 cc. of 16 per cent gamma globulin intramuscularly, it was his opinion that s-agammaglobulinemia was indicated by complete lack of the slow gamma 2 component, and that the amount of fast gamma 2 and gamma 1 components present could not be explained by the administered gamma globulin. The marked increase in alpha globulin was consistent with acute illness. Special stains performed by Dr. Wolfson for distribution of serum lipids, neutral polysaccharide, acid mucopolysaccharide, amyloid and other substances appeared normal.

An excised inguinal lymph node showed an extreme degree of reticuloendothelial hyperplasia which largely obliterated the normal lymph node architecture. (Fig. 5.) Non-caseating granulomas and multinucleated giant cells were observed.

Needle aspiration biopsy of the liver was attempted



5A 5B 5C

FIG. 5. Section of inguinal lymph node, showing extreme degree of reticuloendothelial hyperplasia which largely obliterates normal lymph node architecture. In (A) is a lymphoid follicle with active germinal center. Occasional multinucleated giant cells are seen within areas of reticuloendothelial hyperplasia (B). A discrete granuloma is seen in (C). Hematoxylin and eosin, × 39 (A), × 127 (B), × 63 (C).

on two occasions through the tenth intercostal space in the mid-axillary line. Both specimens obtained represented splenic tissue containing scattered small lymphoid follicles without germinal center activity, and occasional small collections of reticuloendothelial cells.

The unexpected finding of a right-sided spleen led to further roentgenographic examinations which revealed the spleen, liver, stomach and duodenum all to be on the right side, leaving only the descending colon and the jejunum in the left side of the abdomen. (Fig. 4.) The lower part of the esophagus turned to the right side and entered the abdominal cavity through a hiatus of the diaphragm close to the midline. The descending duodenum turned anteriorly, and the third or transverse portion was very short. The jejunum, the ileum and the colon, except for a high splenic flexure reaching the left diaphragmatic leaf, were not anomalous. No anomalies of the urinary tract were found on intravenous pyelographic study.

Roentgenographic survey of the skeleton revealed anomalies of skull, spine and left humerus, as well as clubbed fingers. The left humeral osteochondroma has been mentioned. (Fig. 2.) There was a smooth, symmetrical plate-like hyperostosis of the frontal and parietal bones, with sclerosis of the diploe (hyperostosis calvaria diffusa, of Sherwood Moore). (Fig. 1.) A pea-sized density posterior to the neural arch of the atlas was interpreted as representing an independent apophysis of the posterior tubercle (described by Geipel [*1*]). There was a spina bifida occulta of the sacrum, with ossification of a small apophysis in the middle of the otherwise unossified neural arch.

During the patient's hospitalization, conjunctivitis appeared and was controlled with local antibiotic treatment. Parasympatholytic therapy directed at control of the diarrhea resulted in a dry throat, which quickly became transformed into a purulent pharyngitis spreading to involve the larynx and left maxillary sinus, accompanied by fever and leukocytosis. Hemolytic micrococci and Proteus organisms were cultured from the yellow-green purulent exudate, and recovery was slowly achieved with appropriate antibiotic therapy and discontinuance of the parasympatholytic agent.

The patient was successfully treated with 10 cc. of commercial gamma globulin, a 16 per cent preparation of gamma globulin, administered intramuscularly at monthly intervals, together with prophylactic daily administration of 1.0 gm. of sulfonamide. The diarrhea gradually ceased over a period of months, allowing its dietary and symptomatic medical therapy to be abandoned. The colon resumed a normal appearance on sigmoidoscopic and roentgenographic examination. The generalized lymphadenopathy diminished but did not disappear. The pulmonary infiltrations noted on roentgenograms remained, but the lungs presented no auscultatory abnormalities. The pyorrhea, pyoderma and conjunctivitis gradually subsided within a few months of initiation of therapy. During two years of this therapy there have occurred one episode of acute bronchopneumonia and one of acute bronchitis. These two illnesses proved unusually persistent, but responded finally to combined antibiotic and additional gamma globulin therapy.

COMMENT

The interest of this case is that it may shed some light on the question of whether adult agammaglobulinemia is congenital in origin or truly acquired. In a recent review [*2*], the term "acquired" is adopted for adult agammaglobulinemia because the actual state of hypogammaglobulinemia is assumed not to have existed for any length of time prior to the onset of recurring infections. However, there remains the possibility of an inherited basic biologic defect manifesting itself in delayed failure of gamma globulin production. That failure in gamma globulin synthesis is responsible for the deficiency in adult agammaglobulinemia has been indicated by demonstration of a normal rate of degradation of administered radioiodinated gamma globulin [*3*]. The absence of plasma cells is a similar indication of failure of synthesis of gamma globulins.

Most cases of juvenile agammaglobulinemia have been associated with diminution of lymphoid elements, or absence of their germinal centers [*4*]. Many cases of adult agammaglobulinemia, however, have been associated with reticuloendothelial hyperplasia [*5*] and some with granulomas [*6*], as in the present instance. It is in these patients, particularly, that the agammaglobulinemia may be supposed to be truly acquired, as a result of disturbance in gamma globulin formation. However, the finding of multiple congenital anomalies in the present case suggests that the agammaglobulinemia may represent yet another congenital anomaly.

The finding of hypergammaglobulinemia in both parents of the patient reported herein suggests a genetic basis for the hypogammaglobulinemia of the son. Citron [*7*] has reported a similar instance in which both parents of a patient with hypogammaglobulinemia were found to be hypergammaglobulinemic. Such a relationship suggests that the hypergammaglobulinemia may possibly represent the effect of a recessive gene for hypogammaglobulinemia, the latter appearing only in the double recessive inheritance.

SUMMARY

A patient with adult agammaglobulinemia characterized by recurring pyogenic infections, sprue-like syndrome, and reticuloendothelial hyperplasia of spleen and lymph nodes with granuloma formation, was found to have multiple congenital anomalies. This association is taken to favor the possibility that such adult "acquired" agammaglobulinemia may, in fact, represent another congenital anomaly. A hereditary basis is suggested by the presence of hypergammaglobulinemia in both parents.

Acknowledgment: The biopsy specimens of spleen and lymph node were interpreted by Dr. Charles G. Hermann, Chief of Laboratory. Independent electrophoretic studies were contributed by Drs. Robert E. Bolinger, Chi Che Wang and William Q. Wolfson. For the photographs we are indebted to the Medical Illustration Laboratory.

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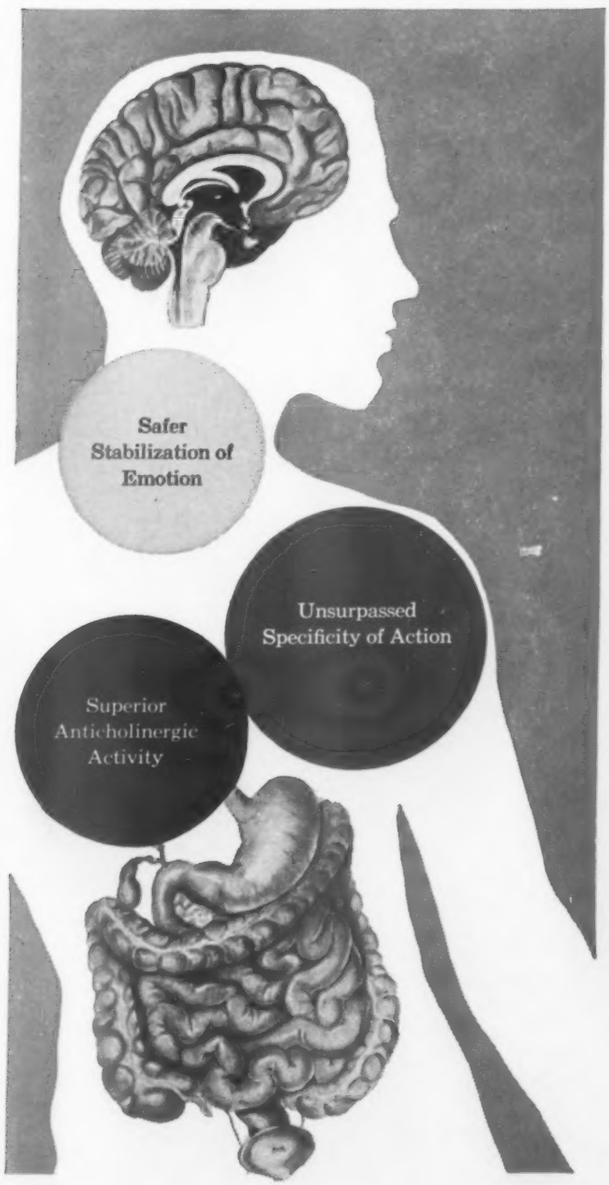
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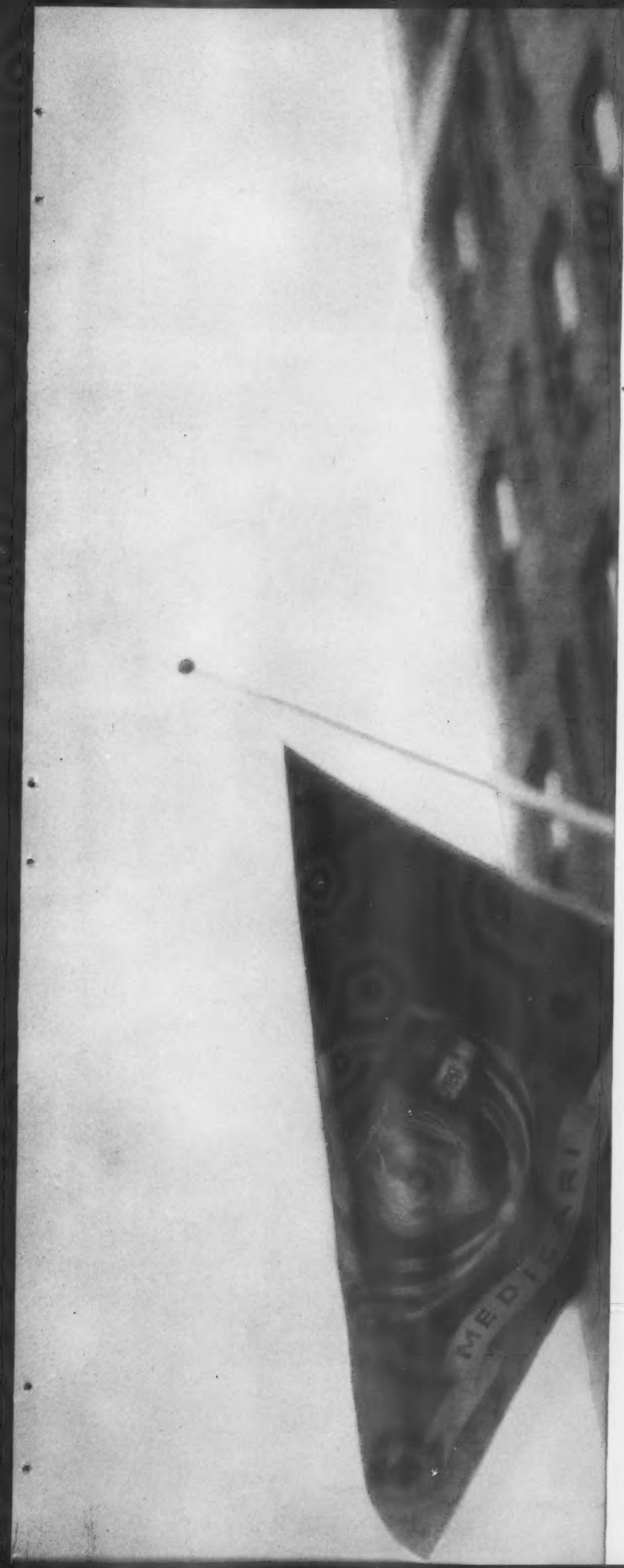
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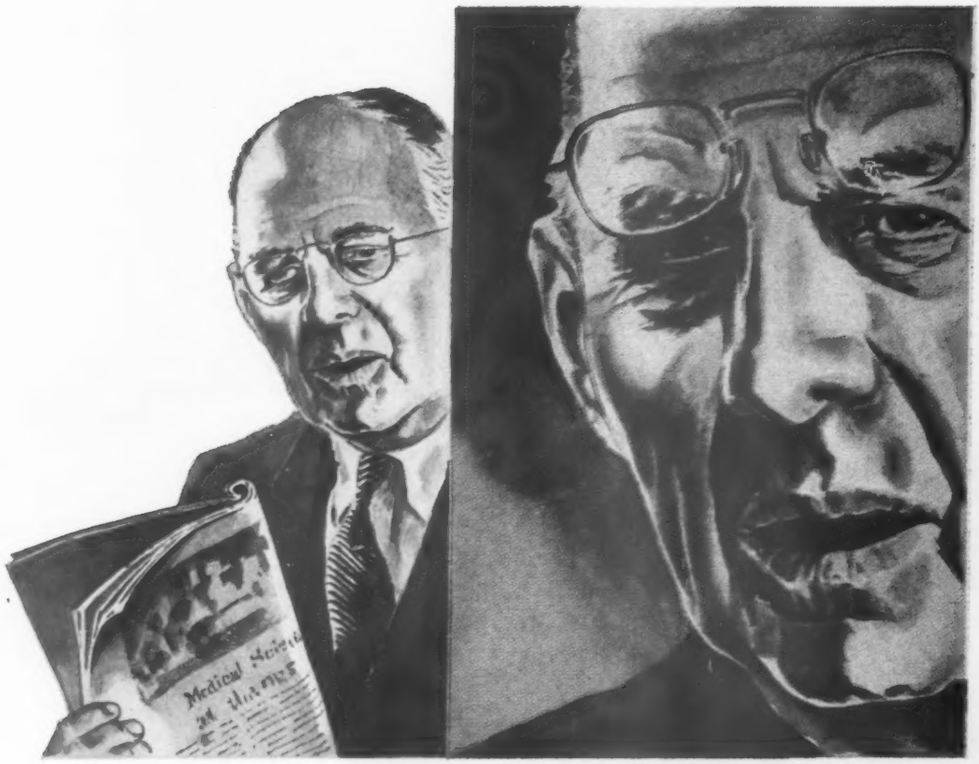
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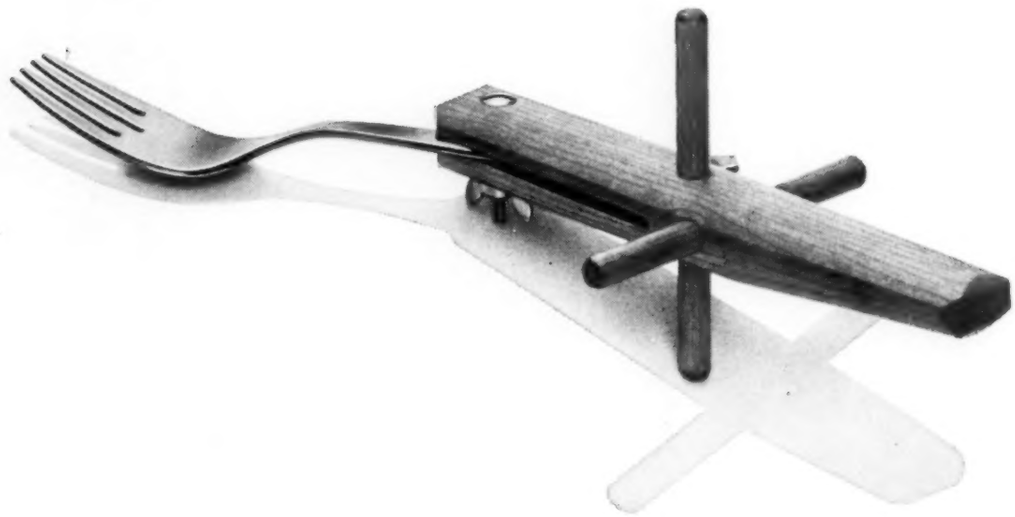


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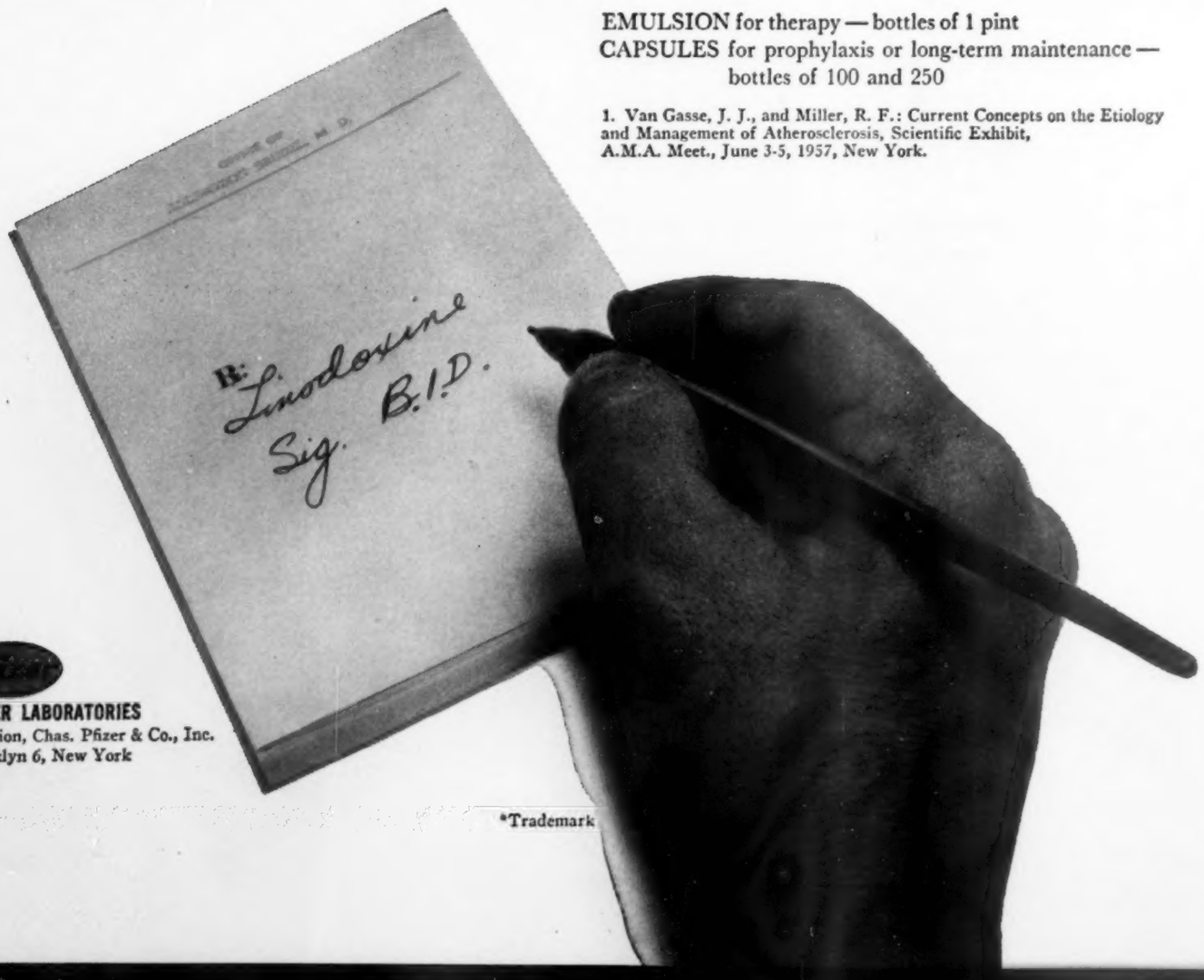
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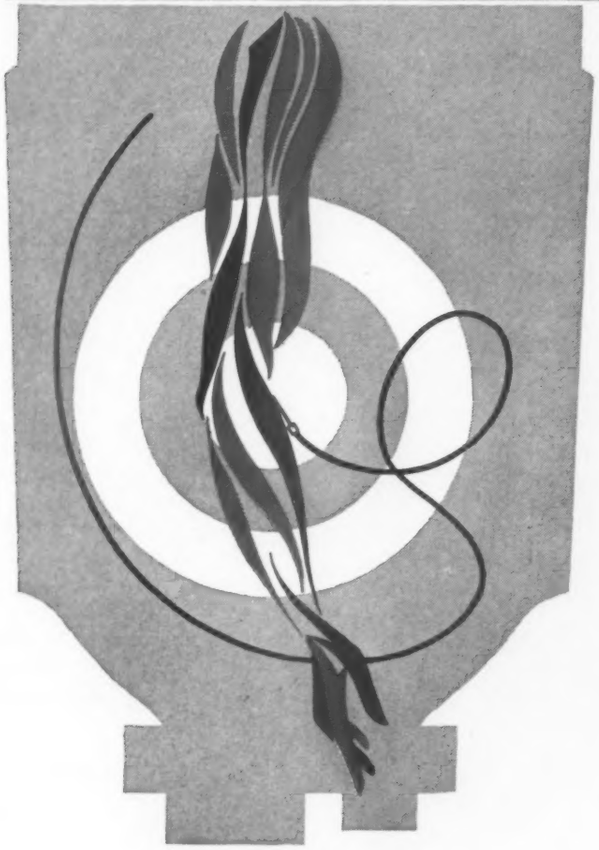


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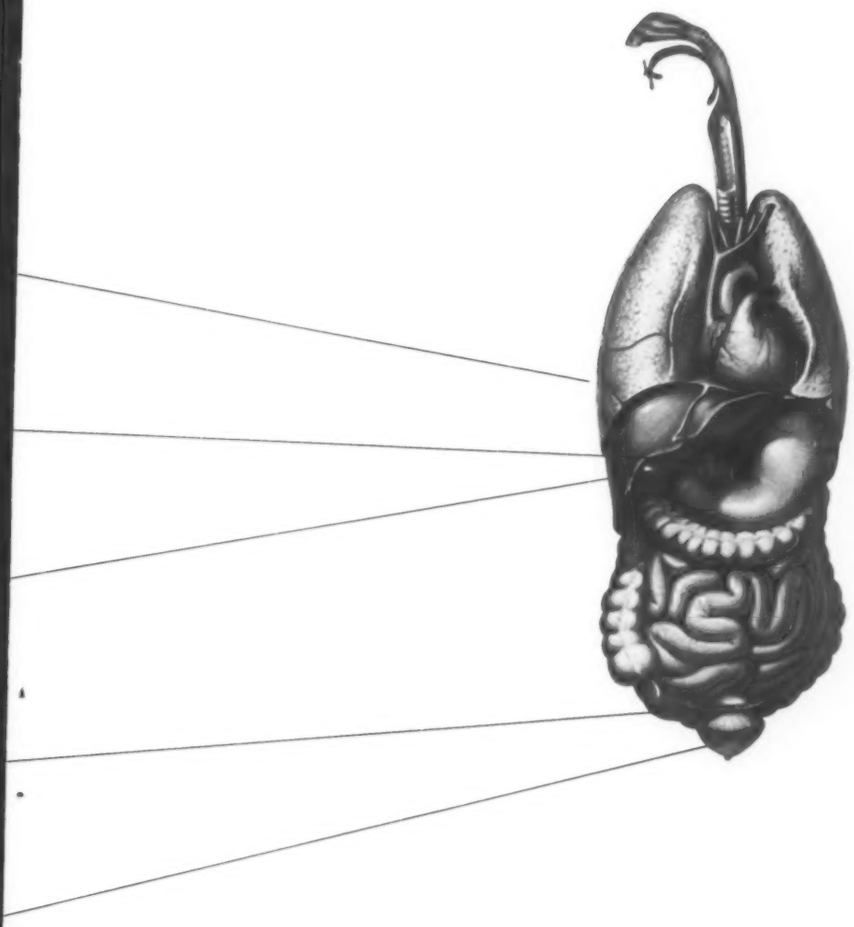
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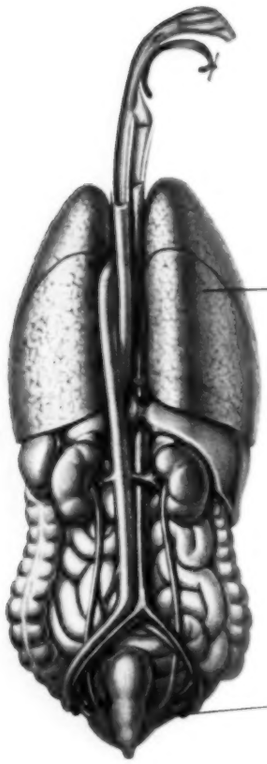


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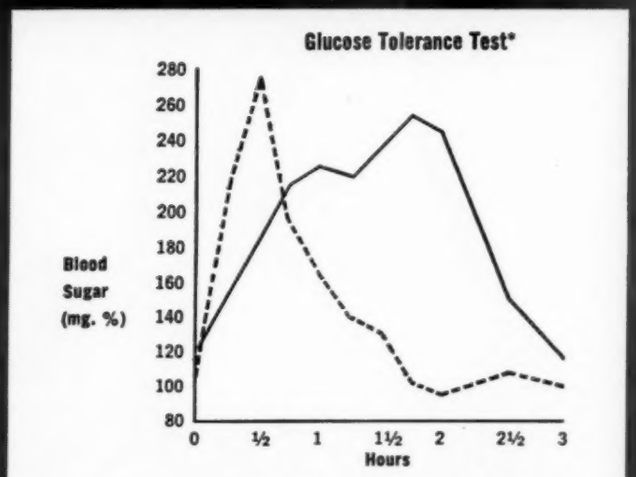
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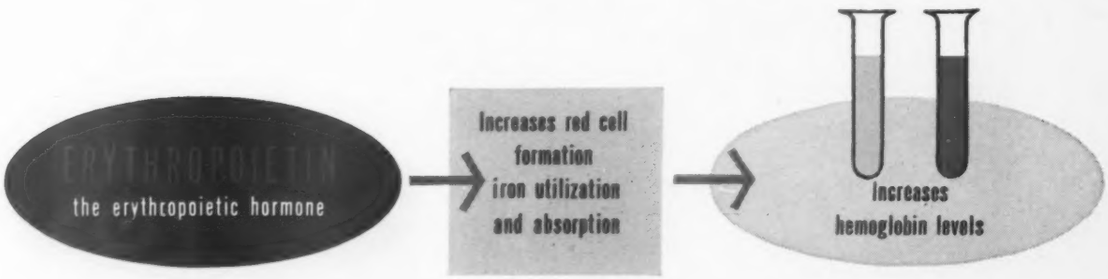
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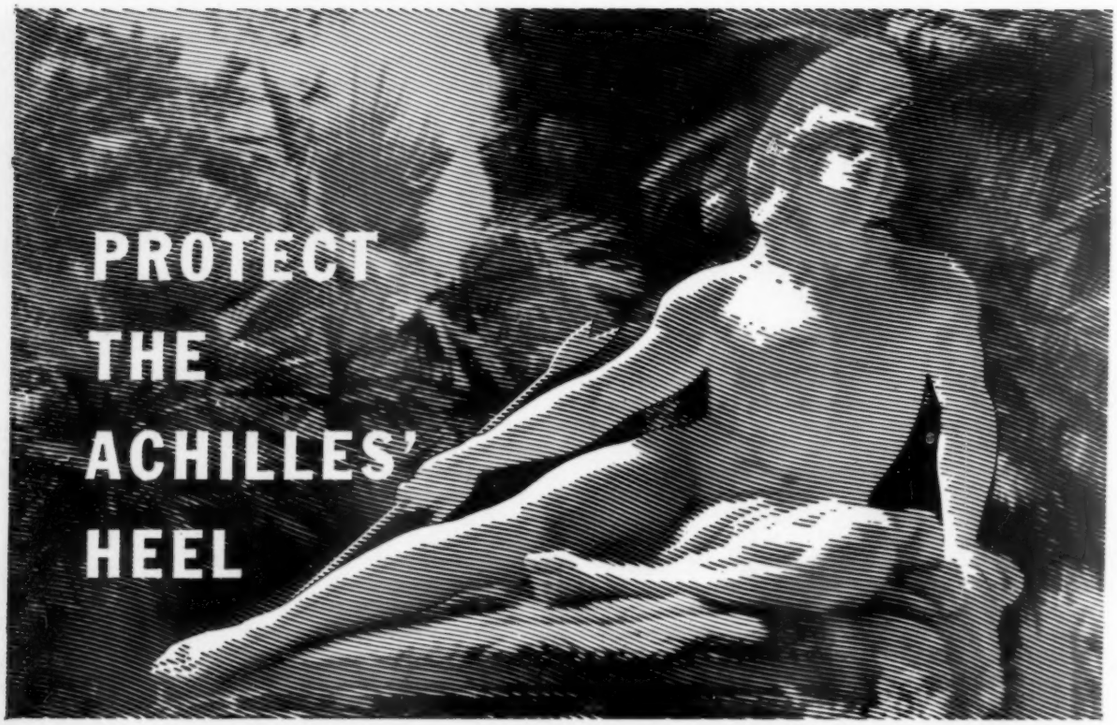
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Supplied: Bottles of 100 tablets.

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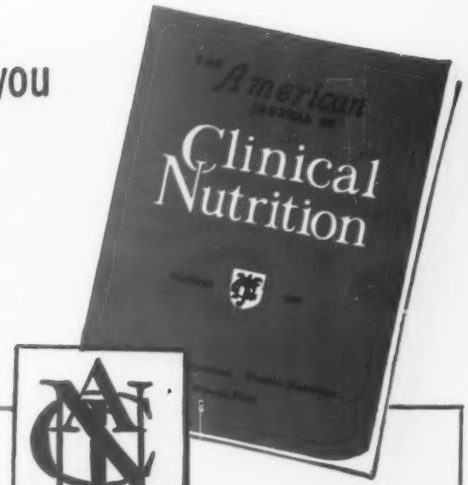
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REFERENCES: (1) Roy, T. E.; Collins, A. M.; Craig, G., & Duncan, I. B. R.: *Canad. M.A.J.* **77**:844 (Nov. 1) 1957. (2) Schneierson, S. S.: *J. Mt. Sinai Hosp.* **25**:52 (Jan.-Feb.) 1958. (3) Hasenclever, H. F.: *J. Iowa M. Soc.* **47**:136, 1957. (4) Rhoads, P. S.: *Postgrad. Med.* **21**:563, 1957. (5) Caswell, H. T., and others: *Surg. Gynec. & Obst.* **106**:1, 1958. (6) Josephson, J. E., & Butler, R. W.: *Canad. M.A.J.* **77**:567 (Sept. 15) 1957. (7) Petersdorf, R. G.; Curtin, J. A., & Bennett, I. L., Jr.: *Arch. Int. Med.* **100**:927, 1957. (8) Waisbren, B. A., & Strelitzer, C. L.: *Arch. Int. Med.* **101**:397, 1958. (9) Holloway, W. J., & Scott, E. G.: *Delaware M. J.* **29**:159, 1957. (10) Murphy, J. J., & Rattner, W. H.: *J.A.M.A.* **166**:616 (Feb. 8) 1958. (11) Neter, E., & Hodes, H. L.: *Pediatrics* **20**:362, 1957. (12) Woolington, S. S.; Adler, S. J., & Bower, A. G., in Welch, H., & Martí-Ibañez, F.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 365.

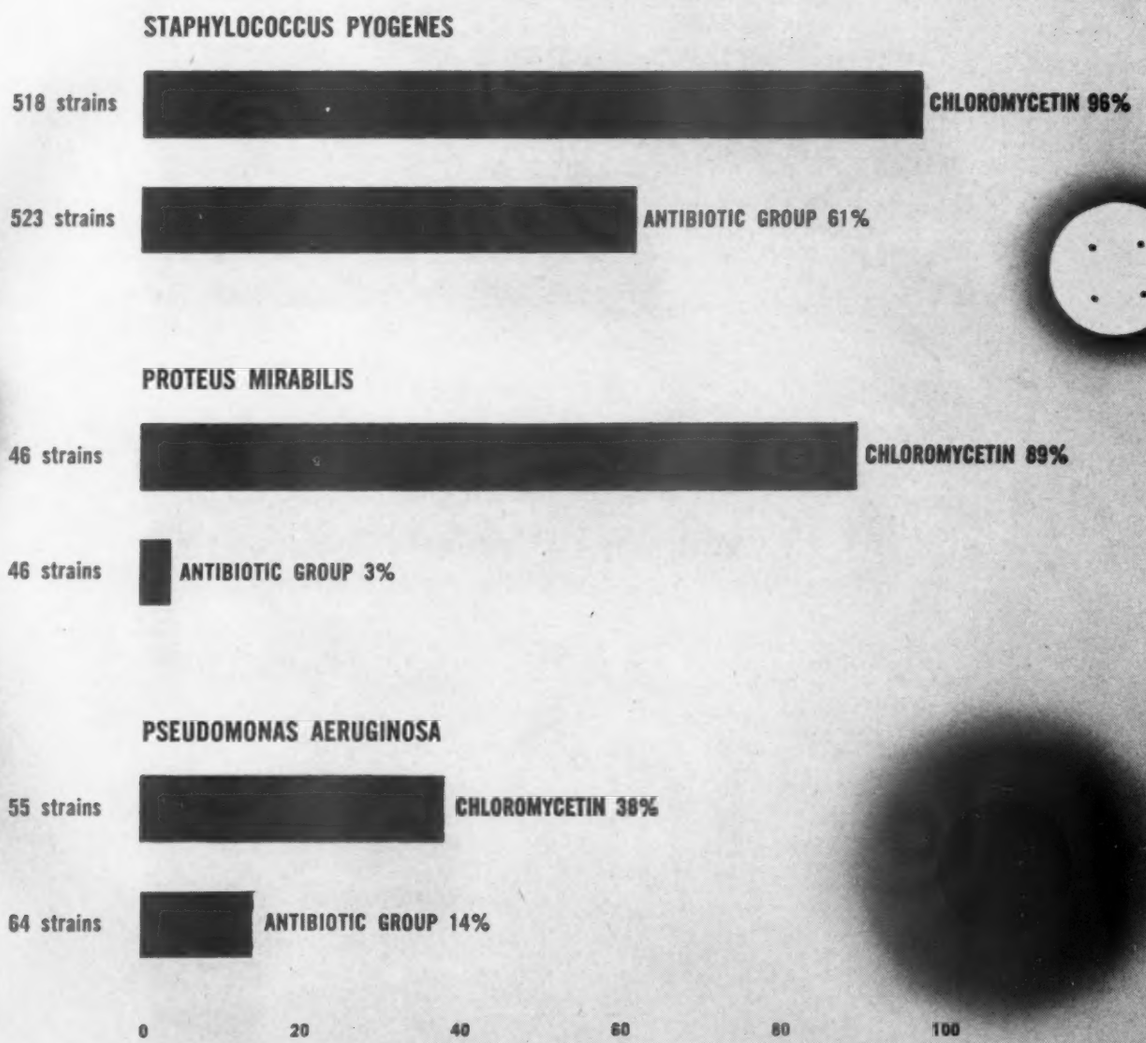
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*Franklin, M., et al.: Chelate Iron Therapy, J.A.M.A. 166:1685, Apr. 5, 1958.
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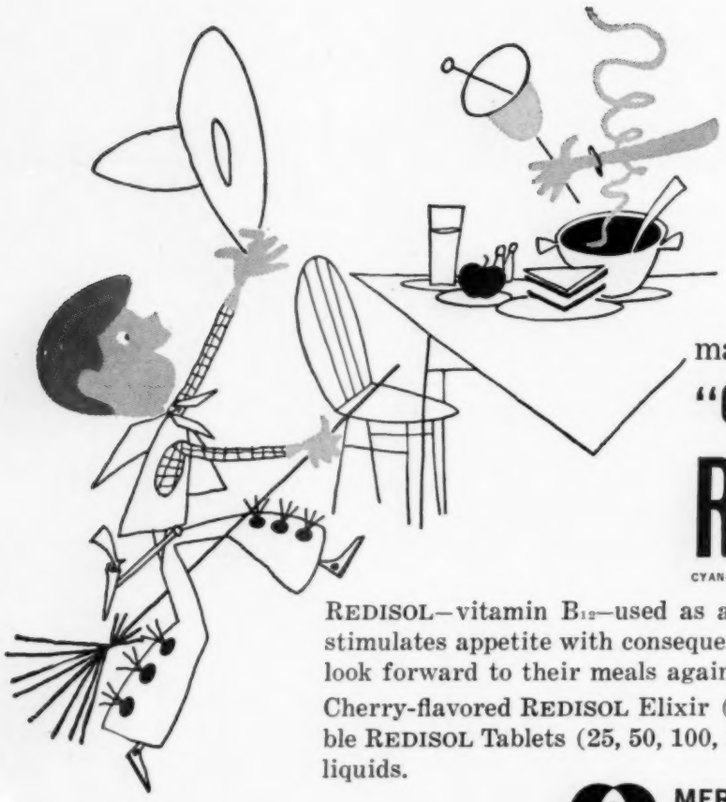
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FORD, R. V., Rochelle, J.B.III, Handley, C. A., Moyer, J. H. and Spurr, C. L.: J.A.M.A. **166**:129, Jan. 11, 1958.

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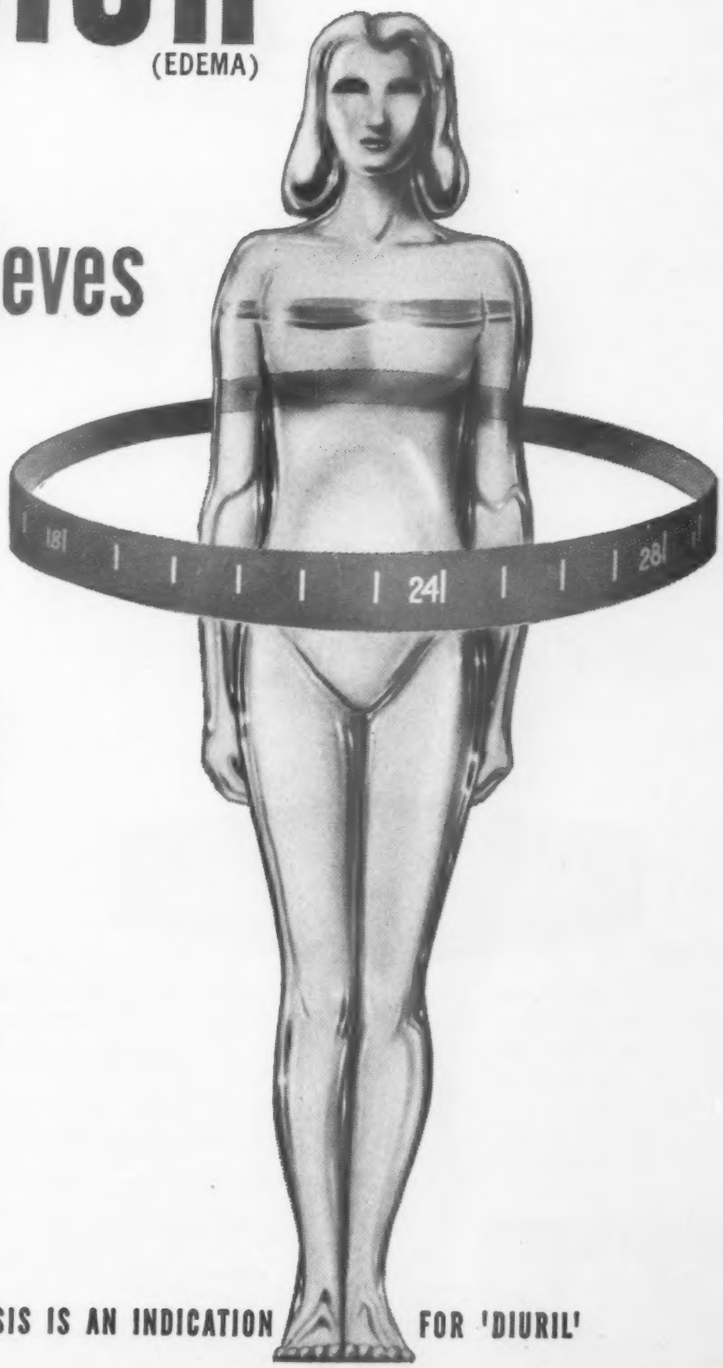
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1. *Eisfelder, H.W.: Am. Pract. & Dig. Treat. 5:778 (Oct. 1954)*
2. *Freed, S.C.: G.P. 7:63 (1953)*
3. *Sherman, R.J.: Medical Times, 82:107 (Feb. 1954)*

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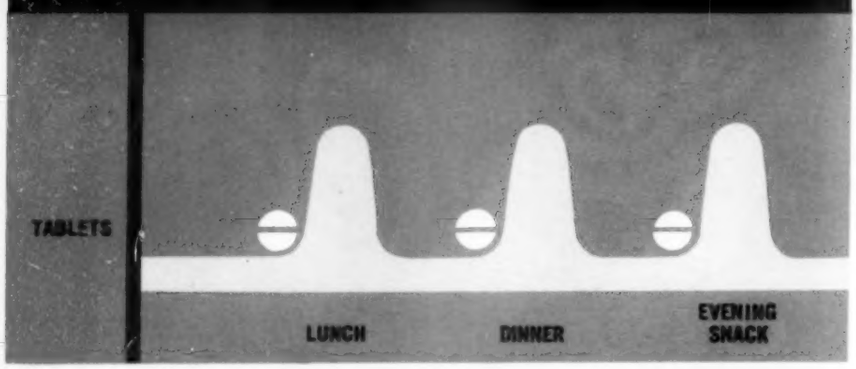
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Goldbloom, A. A., Feinstein, M. A. and Eiber, H. B.: *Am. J. Dig. Dis., 22*:288, 1955.

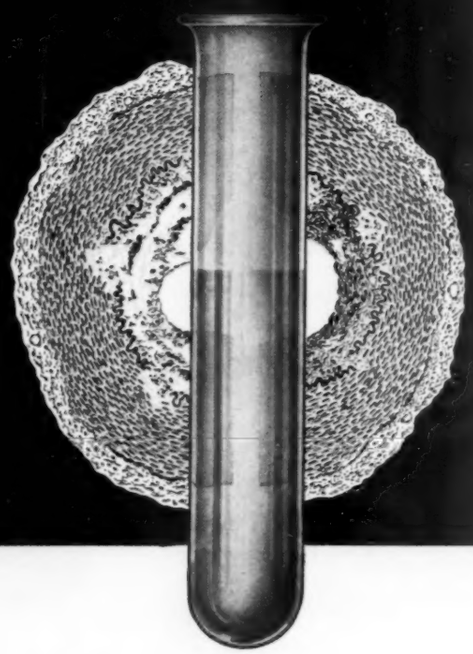
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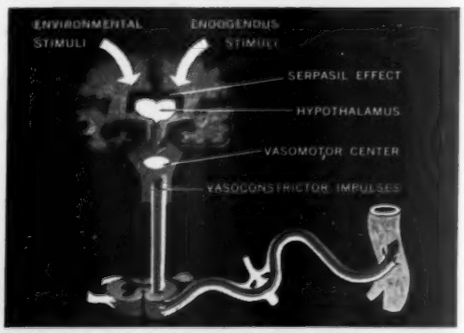
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Ascorbic Acid (C)	50 mg.	Manganese (MnO_2)	0.05 mg.
Vitamin K (Menadione)	0.5 mg.	Magnesium (MgO)	0.15 mg.
Folic Acid	1 mg.	Molybdenum ($Na_2MoO_4 \cdot 2H_2O$)	0.025 mg.
		Zinc (ZnO)	0.085 mg.
		Calcium Carbonate	575 mg.

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SUPPLIED/attractive re-usable bottles of 100 capsules

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Ford, R.V., and Moyer, J.H.: Rauwolfia Toxicity in the Treatment of Hypertension: Some Observations on Comparative Toxicity of Reserpine, a Single Alkaloid, and Alseroxylon, a Compound Containing Multiple Alkaloids, Postgrad. Med., January, 1958.



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*Judson, W. E., Hollander, W., and Wilkins, R. W.: Circulation *13*:664 (May) 1956.

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